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DEVELOPING COUNTRIES AND THE NEW BIOTECHNOLOGY

MARKET ENTRY AND INDUSTRIAL POLICY

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DEVELOPING COUNTRIES AND THE NEW BIOTECHNOLOGY

Market Entry and Industrial Policy

by
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and
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I. Introduction

I.i. What is this document about?

Biotechnology promises to become an effective weapon in fighting such major evils as disease, malnutrition, plagues, energy deficits and pollution. Ergo, no country can afford **not** to consider it as a high priority. However, hardly any industry's future pattern of development is as immersed in uncertainty as that of biotechnology: the stock of basic and applied knowledge in this field is still growing at a much higher rate than the capacity to put it to economic use -- although the difference is presumably diminishing. After all, in and of themselves, scientific achievements should not be expected to bear any simple causal relationship with innovation lead times.

Just as, despite all its marvellous achievements, the "informatics revolution" has failed so far to come to grips with the problem of anemic social productivity growth in the largest capitalist economy--the so-called "Solow paradox" [Abramovitz (l989)]; [Freeman (l989)]--, the "biotechnological revolution" has not yet even begun to help satisfy the needs of the world population to any significant degree.

Biotechnology is also expected to contribute to pervasive and dramatic improvements in social productivity by sharply reducing energy and other input requirements. As we shall see, this potential is still very far from being realized. However, it undeniably remains a distinct possibility.

Will the new biotechnology be taken over, wholly or partly, by large established companies (LECs) with vested interests in earlier technology vintages? Will this result in its potential being largely sterilized, as when advanced microelectronics is applied to let Taylorist and Fordist systems outlive themselves in face of emerging superior forms of social organization? Less developed countries (LDCs) have a vital stake at play with regard to these questions, on which we expect to shed some light.

This document takes stock of the current position of the industry and looks into some of the main determinants of the diffusion of biotechnologies. This is done mainly from the perspective of the LDCs and focuses on matters relevant to industrial policy. Based on this assessment, a suggested agenda for future research efforts is laid out.

Biotechnology consists of a set of enabling tools that make it possible to use the genetic information available in living matter to produce economic value. This document is concerned with the "new" biotechnology, a generic cluster of technologies which comprises recombinant DNA (rDNA) technology or genetic engineering, hybridoma technology or cell fusion, protein engineering and related techniques [1].

This entirely new scientific and technological frontier came into existence as a result of two fundamental scientific breakthroughs made possible by Watson and Crick's landmark discovery of the structure of DNA in l953 [**J. D. Watson** (l968) and **F. Crick** (1974)].

The first one is Cohen and Boyer's invention of a process for DNA recombination patented in l973. The second one is Milstein and Kolher's unpatented invention of a method of antibody-producing hybridoma (or monoclonal antibodies-Mabs) in l975 [2]. A large series of subsequent discoveries in the fields of new bioprocesses and products and protein engineering gave shape to one of the most fertile, dynamic and promising shifts of the scientific and technological frontier in the history of humankind (for a calendar of important scientific and business-related events in the history of biotechnology see Table I).

The "new" biotechnology has taken over the old one and infused it with a completely new perspective. Fermentation, for instance, the key process of the old biotechnology, has now become just one stage of the new, although it still plays a critical rôle regarding cost, efficiency and quality. Techniques such as selective breeding in agriculture and animal husbandry, on the other hand, are likely to be progressively displaced thanks to "shortcuts" allowed for by genetic manipulation.

LDCs' perspectives cannot be considered independently of events in developed countries (DCs). Biotechnology is still in its formative stages and its definite trajectory will be largely shaped in those countries. This means that its future impact on LDCs is subject to a number of uncertainties which can be elucidated only by understanding what is *currently* going on in DCs.

Thus, for instance, the study of entry by LDC firms into biotechnology should benefit from an understanding of entry by DC firms, provided that due allowance is made for structural, behavioral and institutional differences in the economy. Likewise, the understanding of problems such as the linkage between the scientific and engineering development stages, the economics of biotechnology R&D, and engineering and manufacturing matters in downstream processing (involving issues like standards, skills, costs and risks) should help to shed light on LDC prospects and assist in devising appropriate policies.

The understanding of the dynamics of technical change in DCs should also be useful in identifying the valid interlocutors for LDCs: universities; research boutiques; dedicated biotechnology enterprises (DBEs) with hopes of becoming large and integrated corporations; transnationals. This question cannot be answered without assessing the nature of these different actors, their relationship to each other and their respective strategies and likely trajectories. We shall come back to these themes at several points in the text and when discussing the research agenda.

It is not yet quite clear what the technological and industrial trajectory of biotechnology will be, even within the near future. Important scientific, technological, economic and political uncertainties remain. For one thing, not enough is yet known about things such as the relationships between protein structure and functions, the mechanisms of pathogenicity in plants and drug delivery methods.

For another, it is still by no means certain whether biotechnology will give rise to a truly new industry, as was the case with microelectronics, or whether it will be assimilated by already existing industries. The relative competitiveness of the new biotechnology products and processes still remains to be demonstrated, except in the few cases where it has given birth to entirely new products (like Mabs) or has overcome absolute physical and/or cost limits to input availability (to produce insulin, for instance).

One thing is clear, though: there is a discrepancy between the rapid development of the scientific frontier and the rather lagging evolution of the technological and manufacturing frontiers. It will take a great deal of time and resources for the latter to catch up with the former. Biotechnology presents plenty of room for controversy and contrasting views, for it appears to challenge a good deal of the conventional wisdom regarding issues such as the importance of scale, the rôle of basic science in industrial development and the locus and focus of technical change, not to mention ethical issues [3].

This document examines some of these themes with a particular emphasis on the factors affecting the international diffusion of the technology and related LDCs' **industrial** policy issues. **Trade** issues are given somewhat less emphasis than usual in discussions on the subject.

The basic dilemma LDCs face regarding commercial biotechnology is how to avoid entering it too early ... or too late, and how to avoid pursuing wrong leads and dead end tracks. Getting a foot into biotechnology at a point too far removed from the market or too dependent on price sensitive products in highly competitive and risky markets may not, *per se* , be a sensible approach. Unfortunately, abstract moral and social concerns about the impact of this emerging industry, no matter how legitimate, are just not enough to provide guidelines for industrial policy.

I.ii. Approach and methodology

This document is focused on the economic significance of biotechnology. For this reason, it makes a point of being quite strict all along regarding the concept of "entry". Scientific and technological achievements, however valuable and promising, have to follow a difficult path towards commercialization. Short of that, their economic significance will remain negligible, despite all possible hype and excitement among scientists and venture capitalists (or governments) prepared to afford long and uncertain innovation lead times.

Chapter II is devoted to a review of the evidence as to what is the actual state of diffusion of biotechnologies across a broad range of applications and the perspectives ahead in this regard. Because of reasons that have to do with access to information and relative country positions at this point in time, the text refers mostly, although not exclusively, to the US case.

Chapter III consists of an enquiry into several of the most important factors that affect the timing of introduction and rate of diffusion of biotechnologies. Thus, it discusses company strategies, scientific, technological and engineering bottlenecks and uncertainties, and barriers to entry and threshold factors (such as scale, regulation, and public opinion). It also deals with the relative competitiveness of biotechnology products and processes.

Chapter IV focuses on LDC entry strategies and related industrial policy issues. It examines some national experiences and singles out a set of themes relating to actual LDC prospects in biotechnology.

Finally, chapter V provides some directions for further research. First it identifies researchable issues and then puts forward some ideas on background and policy-oriented research projects. It also contains a concrete proposal for further international cooperative action aimed at facilitating LDC entry into the new industrial frontier.

Because of the rapid succession of new scientific discoveries, technological applications and market entries (and exits), relying just on learned journals and books would not have allowed us to present an updated view of the situation of the industry. Therefore, it has also been necessary to resort extensively to the technical literature and diverse sources covering current events.

For example, as this text is being written, a December l989 issue of the journal *Cell* includes an article reporting the discovery by scientists at the Whitehead Institute for Biomedical Research (M.I.T.) of the so-called RAG-1 gene, believed to be crucial in the development of human immune defenses. This discovery may led to a better understanding of some genetic diseases in which the body's defense systems fail, although it is far too early to tell what practical applications may result.

In a closely related development, a December l989 issue of *Nature* reports the discovery by a group of scientists at Kyoto University of a gene believed to be central to the genetic recombination process in bone marrow cells.

Also in l989, the molecular basis of muscular dystrophy and cystic fibrosis were elucidated, opening the door for new therapies.

These advances, along with many others that keep succeeding each other at an amazing pace, continuously alter the scope and extent of the knowledge base and the uncertainties that guide the direction of scientific and technological efforts and the prospects for commercial exploitation in the biotechnology field.

This document is not intended to be exhaustive in its coverage but, rather, it privileges the treatment of some issues and selectively highlights qualitative gaps in understanding and knowledge that should be filled for the benefit of research and policy-making in LDCs.

Our main purpose in what follows is not to establish absolute truths but, rather, to set into motion a meaningful debate on these emerging issues and, hopefully, to inspire effective action, so that the benefits of biotechnology can be reaped by those who need them most.

From an editorial point of view, we regret to have had to resort to the use of some terms and acronysms that may at times make the readers feel a bit uncomfortable. But so far we have failed to find appropriate substitutes. Some of these terms, like "new" [biotechnology] and "dedicated biotechnology enterprises-DBE" we have not coined: the first is extensively used in the literature on biotechnology while the second we have adopted from the US Office of Technological Assessment. We acknowledge parenthood on the perhaps unlikable LEC (large established enterprise). It would not have been appropriate to replaced it by TNCs or MNCs since in biotechnology the international scope of companies is unrelated to size. We have define all these terms when they first appear in the text.

Finally, we would like to thank Brent Herbert-Copley and his colleagues at IDRC for their comments and suggestions. The responsability for the opinions submitted in this document lies only with us.

Montreal, April 1990

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Table1

Calendar of Important Events in the History of the "New" Biotechnology

Year	Science	Business
1955	Watson & Crick-Double Helix	
1970	First synthesis of a gene (non functional)	
1971	Restriction (cutting) enzymes discovered	Cetus founded
1972	Initial work with embryo transfer	
1973	Cohen & Boyer perfect genetic engineering techniques to cut and paste DNA (using restriction enzymes and ligases) and reproduce the new DNA in bacteria	
1975	First Mabs produced Asilomar conference (moratorium on genetic engineering research)	Agrigenetics founded
1976	DNA sequencing discovered First working synthesis gene	Genentech founded
1977	First expression of human gene in bacteria Methods for reading DNA sequence using electrophoresis discovered	Genex founded
1978	High level structure of virus first identified Recombinant human insulin first produced	Biogen and Hybritech founded
1979	Human growth hormone first synthesized	Centocor founded
1980	US Supreme Court concludes lifeforms are patentable-Chakrabarty patent	Genentech IPO; Amgen, Calgene and Genetic Systems founded
1981	Gene synthesizing machines developed	First Mab kit approved Cetus, Genetic Systems and Hybritech IPO's Applied Biosystems, Chiron Genetics Institute and Xoma founded
1982	Rat gene transferred into mice First synthesized vaccines	FDA approves first rDNA product for use-Human Insulin (Humulin)
1983	First artificial chromosone First field test with altered bacteria is delayed First markings for inherited diseases found in genes	First sales of rDNA product-Humulin Amgen, Applied Biosystems, Biogen and Chiron IPO's
1984	Technique for rDNA fingerprinting discovered First genetically engineered vaccines	

1985	Genetic markings found for kidney disease and cystic fybrosis	FDA approves human growth hormone- second genetically engineered drug Bristol acquires Genetic Systems, Lubrizol acquires Agrigenetics
1986	First field trials of genetically engineered plant-tobacco	FDA approves first genetically engineered vaccines-Hepatitis B Eli Lilly acquires Hybritech Calgene, Genetics Institute and Xoma IPO's
1987	First field trials of a genetically altered bacterium	Stock market crash t-PA approved
1988	First US patent for a vertebrate-a transgenic mouse	FDA enacts accelerated regulatory process for products combating terminal diseases
1989	First field trial of a recombinant viral crop protectant	FDA approves EPO IL-2 approved in parts of Europe

Source: Burrill (1989)

Notes

1: For a discussion on alternative definitions of biotechnology see, among others [OECD (1989)].

2: Nobel prize winner C. Milstein (who left his country of origin--Argentina-- for England in 1968 because of oppressive conditions impeding creative scientific work), actually sought to attract the interest of the British government in prospects for patenting and industrial applications connected with his breakthrough. He was kindly sent back to his lab with the argument that if his invention of the Mabs really had any economic value at all, private capital would take care of it in due time without any need for government involvement. And it certaintly did!.. But not precisely to strengthen British leadership in the field. The invention became knowledge of the public domain and was taken advantage of mainly in the US. In [Hudson (1989)], it is reported that Milstein's Laboratory of Molecular Research has recently come up with a new breakthrough, called "single-domain antibodies" that promises to become a basic tool in biotechnology. It consists of a laboratory technique that can make key parts of animal antibody molecules in as little as three days, as compared with today's most common technique that takes a month or more.

3: As we shall see below, often one comes across strongly diverging views as to how "Schumpeterian" the biotechnology industry is or how appropriate it is for LDCs. Sometimes, these discrepancies stem from unwarranted extrapolations or from a poor understanding of the problems of invention and innovation. But they also have to do with the fact that it is still much too early to try to pass definitive judgement on many of the issues concerned. For an elaboration on this see [Sercovich and Leopold (forthcoming)].

II. State of and Trends in the Diffusion of Biotechnology

II.i. Introduction

Biotechnology comprises a pervasive set of enabling technologies with a broad scope for potential industrial applications. These range from pharmaceuticals, agriculture and animal husbandry to energy and mining, through chemicals, food processing, textiles, waste management, forestry and exploitation of marine resources.

The timing of introduction and rate of diffusion of biotechnologies differ widely among sectors. The diffusion rate is the highest in pharmaceuticals, followed by chemicals and agricultural applications with the rest far behind. Within pharmaceuticals, the diagnostics sector is more advanced than therapeutics and therapeutics, in turn, is more advanced than preventive applications. Within chemicals, specialties are more developed than commodities. Within agricultural applications, herbicide-resistant plants are more advanced than biopesticides while animal health care is more advanced than transgenic animals.

The above is a result of differences in policy priorities, the state and evolution of the knowledge base, the rôle of the regulatory environment and public opinion, the relative competitiveness of biotech processes and products and a host of other factors to be examined in chapter III.

We have already pointed out in the Introduction that the scientific knowledge base is growing at a faster rate than the use of such knowledge in practical applications. However, it is almost certain that such an accumulation of a critical mass of basic and applied knowledge will eventually give rise to epoch-making technological and commercial breakthroughs, possibly involving, among other things, a shift away from anti-cancer chemoterapies and agrichemicals. But this is highly unlikely to happen before the turn of the century. In the meantime, the structure of the "industry" will probably become pretty well defined. It will, in all likelihood, take a multiple, application-sector focused, hub-like shape, centered around a rather limited number of LECs serving as nexus among large numbers of research boutiques, DBEs operating in niche markets and research institutions, through a complicated network of financial and technological arrangements.

II.ii. State of diffusion

II.ii.i. General Assessment

Table 2 shows the pattern of concentration of R&D efforts according to type of company. Altogether, 39 per cent of DBEs and 37 per cent of LECs are focused on health-care related fields. The other types of applications come far behind. It is worth noting that nearly 20 per cent of DBEs are involved in intermediate input and hardware supplies (reagents, cell cultures, equipment). The data is based on a sample comprising 296 DBEs and 53 LECs. In the case of DBEs it probably covers around one third of the universe. The coverage is much higher in the case of LECs.

Table 2

Areas of Primary R&D Focus by Biotech Companies
(in number of companies)

Research Area	DBEs # (%)	LECs # (%)
Human therapeutics	63 (21%)	14 (26%)
Diagnostics	52 (18%)	6 (11%)
Chemicals	20 (7%)	11 (21%)
Plant agriculture	24 (8%)	7 (13%)
Animal agriculture	19 (6%)	4 (8%)
Reagents	34 (12%)	2 (4%)
Waste disposal/treatment	3 (1%)	1 (2%)
Equipment	12 (4%)	1 (2%)
Cell culture	5 (2%)	1 (2%)
Diversified	13 (4%)	6 (11%)
Other	31 (18%)	0 (0%)
Total	296 (100%)	53 (100%)

Source: USOTA, l988, b.

Private investment in the US goes mainly to health care applications (75%) and to agriculture (16%). Out of an estimated cumulative $4 billion raised by DBEs, 80% went to ten enterprises [USOTA (1988.b:10)].

II.ii.ii. Pharmaceuticals

The rhythm of introduction of bio-pharmaceutical products has accelerated since l986, particularly with regard to natural proteins and peptides (insuline, human growth hormones, interleukines, growth factors, tissue plasminogen activators) [1]. Emphasis is currently focused on diagnostics and immunology. However, progress in reaching the market is taking place much less rapidly than expected.

Altogether, there are only eight products on the US market. They are human insuline; human growth hormone; alpha interferon; tissue plasminogen activator; erythropoietin; Factor VIII:c; a MAB murine; and a recombinant vaccine against hepatitis B (see Table 3 on the next page).

The number is slightly higher in Japan, including also gamma interferon, products "8" and "9" (for lymphokine), "Bio-3" (an antidiarrheal), and a luteinizing hormone-RH analog (antitumor).

In Europe the number of products is also somewhat higher than in the US, including, in addition to those already approved in the US, other types of interferon; 5 different types of interleukines; some peptides; tumor necrosis factor; and growth factors. Some of these products are already in second or third generation, improved through genetic and protein engineering techniques.

In addition, there are over 300 diagnostic tests on the OECD markets.

Total biotechnology-based health care product sales on the US market for l989 are estimated at about $1 billion, therapeutic products and vaccines accounting for around two thirds of that figure and human diagnostics for the remaining third [*Chemicalweek* (l989.c)] [2].

Currently, there are over 1,000 different companies and groups pursuing Mab-based applications in the world market. Some 20 companies account for 75 per cent of the US diagnostic reagents market. One of the leading suppliers in the *in vitro* segment is Abbott, which introduced over 70 new diagnostic products just in l986. Other important rivals are Baxter, Becton Dickinson, Leeco Diagnostics, which markets over 30 basic test kits, and Eli Lilly, which strengthened its presence in the market through the acquisition of DBE Hybritech in l986. Although there are some DBEs in the *in vitro* segment (like Monoclonal Antibodies Inc.), their presence is more conspicuous in the *in vivo* segment. Here, DBEs like Centocor, Cytogen and Damon compete with LECs such as Bristol-Myers, which is using Mabs in drug delivery systems [Koenig (l989:7)].

New drugs of biotechnological origin already account for a disproportionately high share of total new drugs introduced--if normalized by relative sales value. And this trend is likely to become even sharper [Sercovich and Leopold (forthcoming)].

Table 3

Genetic Engineered Human Therapeuticals and Vaccines and MAB Products on the US and Japanese Markets (I989)

Product	Indication	Company
1. Human Insulin	Diabetes	Elli Lilly (USA) Shionogi (J)
2. Human Growth Hormone	Dwarfism in children	Elli Lilly (USA), Genentech (USA) Sumitomo (J) Yamanouchi (J)
3. Alpha Interferon	Hairy-cell leukemia, AIDS-related Kaposi's sarcoma, genital warts	Schering-Plough (USA), Hoffman-La Roche (USA) Takeda (J), Green Cross (J), Hayashibara (J), Toray (J), Mochida (J)
4. Gamma Interferon	Antitumor	n.a. (J)
5. Mab murine	Kidney transplant rejection	Ortho Pharmaceutical (USA)
6. Tissue Plasminogen Activator	Myocardial Infarction	Genentech (USA)
7. Erythropoietin	Dyalisis anemia	Amgen (USA)
8. Factor VIII:C	Hemophilia	Armour (Rorer) (USA), Baxter Healthcare (USA)
9. Hepatitis B vaccine	Haemophilus influenza B	Merck (USA), Praxis (USA), Banyu (J), Shionogi (J)
10. "8"	Lymphokine	n.d.
11. "9"	Lymphokine	n.d.
12. Luteinizing hormone-RH Analog	Antitumor	Takeda Chemicals

Sources: Based on: PMA (I989); USOTA (I988); *Biotechnology Newswatch* (I989); *Chemicalweek* (I989.c); Prudential-Bache (I989); *Business Week* (I989.b)

Although European governments have been quite active in biotechnology, the lack of development of venture capital markets (except in the UK) and great disparities in the regulatory environment (see section III.iv.iii.) place European countries at a relative disadvantage vis-à-vis the US. However, European pharmaceutical and chemical companies, as well as their Japanese counterparts, have been very active in using their financial leverage to take advantage of sciencific, technological and manufacturing progress in the US through an intricate network of inter-company alliances and links with research centres and universities (see section III.iii.).

As mentioned, there are only 8 genetically engineered and Mab products on the US market. Fully 17-odd companies are sharing in the returns by virtue of of alliances set up earlier on through the various stages from R&D to marketing by means of instruments such as research contracts, licensing agreements, and agreements concerning the carrying out of clinical trials, manufacturing and/or marketing.

A rough comparison between development costs (around $120 million) and market size for each of these biologicals (on average, also around $ 120 million, the returns on which, in several cases, have to be shared by two or more suppliers) already suggests a relatively overcrowded market resulting from an unusual swarming process [3]. In addition, some further 35-odd companies are expected to enter the market **for the same products** within the next few years, as soon as they finish their clinical trials and the FDA licenses them. [For further treatment of this swarming phenomenon at the product and company level and its implications for the industry, see Sercovich and Leopold (forthcoming)].

Current investments in biotechnology rely heavily on automation equipment, including automated DNA and protein/peptide synthesizers and sequencers. This type of equipment alone is expected to account this year for over $150 million (R&D labs account for over 90 per cent of the market) [4]. Some market sub-sectors are growing at rates of over 100 per cent per year. The current biotechnology market for all lab equipment and supplies in the US is estimated to be close to $2 billion [Gray (l989:12)].

II.ii.iii. Agriculture and Animal Husbandry

Biotechnology is expected to produce plants that are resistant to disease and plagues, withstand environmental stress, have accelerated rates of growth and increased nutritive value, produce their own nitrogen fertilizer and even grow proteins [5]. However, deficiencies in the knowledge base, lack of investment, and regulatory and public opinion-related uncertainties (see section III.iv.iii.), have held back the rate of progress in agricultural applications.

No genetically engineered plant or plant inoculant has yet been approved for full-scale commercialization.

Applications of biotechnology to plant agriculture fall into two basic categories: (i) genetically engineered plants and crops and (ii) genetically engineered microorganisms applied to plants and crops.

In the first case, rDNA methods are used to confer new traits upon plants. These traits may be obtained through single or multiple gene transplants. In single gene transplants, plants are coded for resistance to, among others, insects, plant diseases and herbicides. These traits are reproduced in offspring. In multiple gene transplants, plants are coded for, among others, higher yields, nitrogen fixation capability, improved nutritional value. Prior to the development of recombinant methods, new traits were also obtained in plants, but through breeding techniques, which continue to be used.

Genetically engineered microorganisms designed for plant use include microbial-based pesticides and herbicides as well as microorganisms that increase nitrogen take up or delay frost damage in crops. In most instances, recombinant microbial products have been preceded by naturally occuring micro-organisms and chemical control methods, which are still being used. Thus, as with genetically engineered plants, the new products and processes are often substitutes. Their relative competitiveness is assessed further on (see section III.v).

Different techniques have been developed to apply recombinant microbial inputs to plants. These include coating the seed, vaccinating the seed, applying the microbes to the seed-furrow, and mixing them into the seed-bed. Although these methods do not necessarily involve biotechnology, the efficacy of the engineered microbes in performing their designated functions depends in part on the choice of applications.

Much of the basic technology involved in producing transgenic plants and microorganisms is becoming widely used (gene splicing, gene sequencing, gene synthesis, etc.), while other areas, such as gene delivery systems, are in a more incipient state and receive much attention.

The US EPA has reviewed and approved a wide variety of field research applications. In the two years that the US Department of Agriculture's Animal and Plant Health Inspection Service' guidelines for regulating genetically engineered plants and plant pests have been in effect, over four dozen genetically engineered plants have been successfully field tested [Godown (l989:1096)].

Some 6 engineered microorganisms had undergone field testing in the US as of late l989. Figures for Europe are similar, although there things are proceeding somewhat more slowly because of greater environmental hurdles (see section III.iv.iii.). The summer of l989 saw an increase of outdoor trials over all previous growing seasons. [Schneider (l989:A1)]; [*The New York*

Times (1989.b)]; *The Economist* (1989.b:16)]; [Pimentel et al. (1989):606-614]; [Burrill (1989:215)]

In the case of genetically engineered plants, altered species include tobacco, corn, cotton, soybeans, tomatoes. Field tests have been doubling each year since 1986, when tobacco (the so-called "laboratory mouse" of plant science) became the first transgenic crop to undergo outdoor experimentation . In the summer of 1989 , outdoor testing included pest-resistant tobacco, corn and tomato plants and herbicide-resistant tomatoes, tobacco, cotton and soybeans plants. Single gene transplants conferring insect, plant disease and herbicide resistance and the reproduction of such traits in offspring have been successful in early field trials [US Department of Commerce (1989:19-3)]; [Schneider (1989.b):A1].

Progress has been particularly rapid in the engineering of herbicide resistant or tolerant plants. Insofar as the target sites of the major herbicides are generally known and tend to be single enzyme, they are comparatively easy to alter. Active herbicidal compounds against which crop tolerance has been conferred include glyphosate (found in the herbicide Roundup), sulfometuron methyl (Oust), chlorsulfuron (Glean), AC 243,997 (Arsenal), Phosphinothricin (BASTA), triazine (Atrazine). [Botterman and Leemans (1988)]; [Jones and Lindsey (1988)].

As indicated, a rather limited number of agriculturally useful genetically engineered microorganisms have thus far undergone small-scale field testing. Field trials in the summer of 1989 included an engineered viral spray and pesticidal recombinant corn and rice vaccines [US Department of Commerce (1989:19-4)]; [Burrill (1989)]; [Allen (1989.b)].

Just as in the case of plants, the engineering of herbicide resistant traits has been an area of relatively intense activity, so with microorganisms much attention is being focused on recombinant biopesticides (using both living and killed engineered microorganisms) and on the techniques used to apply them to plants. Biopesticidal seed vaccine and the related vaccination technology appear to be particularly promising and, as mentioned, are in the field trial stage.

Recombinant microbial control agents can be used in combination with chemical pesticides and herbicides. Innovations in this area include a bioherbicidal technology combining bacteria toxic to weeds with low doses of chemical herbicides; field testing is scheduled to begin this year. [Allen (1989.a)].

Progress is being made in the field of gene delivery systems, notably through biolistics, that introduces DNA directly into plant cells and tissues by using microprojectiles and without the need for plasmid vectors. At present, biolistics is being used commercially on a small scale, pending further improvements in both the apparatus and the process itself. Once refined, this system, along with other gene transfer methods presently being developed (eg. electrophoretic transfection), should make it possible to simplify cell transformation and to broaden the range of recombinant plant species [Sanford (l988:299-302)]; [Schneider (l989.b)]; [*Agricell Report* (l989.a)].

Although a patent has been granted on a process for creating genetically engineered animals (see Table I.1.), significant bottlenecks in the engineering of large animals, related, among others, to the low efficiency of embryo transfers, is hampering development in this sector [Andrews (l989)]; [Green (l989:558)].

As in the area of plants, the use of biotechnology in animal husbandry includes both direct genetic intervention on the organism and the application of modified microbial products to the organism. Thus, animal applications involve the genetic engineering of farm animals and the use of recombinant veterinary health care products.

Attempts are being made to confer traits upon livestock that improve production efficiency, product quality and disease resistance, allow for the testing of human disease and new drugs, and make possible the use of transgenic sheep, pigs and cows as "bioreactors" [Van Brunt (l988:1149)]. In the area of veterinary health care, new products are expected to include a host of hormones, vaccines, diagnostic tests and therapeutics [US Department of Commerce (l989:19-3)]; [Bishop (l989)]; [*The New York Times* (l989.d)].

Sales of biotech products in the agricultural segment are estimated at around $50 million for 1989. Products currently on the market include biopesticides, such as a *Bacillus thuringiensis* -based pesticide for the Colorado potato beetle (in this case still on an experimental basis); animal health-care products, such as scours and pseudorabies vaccines; and diagnostics [*Chemicalweek* (l989.c:31)].

More than half of a sample of 170 companies performing genetic research in the US were focusing on veterinary diagnostics in l987. At least 25 of them were developing new animal/poultry vaccines [Department of Commerce (l989)]. Three recombinant animal vaccines were commercially available and 15 more were undergoing field testing in l988 [Andrews (l989)]; [Green (l989:558)].

Of most immediate commercial interest, however, is the bovine growth hormone (bGH), also known as bovine somatotropin (bST). It enhances the efficiency of milk production in dairy cows, with yield increase estimates varying between 10 and 40 per cent [Kuchler and McClelland (l989)]. After having been in field trials since l982 (including widespread testing in Africa, Asia and Latin America), bGH is now awaiting approval for commercial sale by the US FDA. Pending final licensing, expected for this year, milk from experimental herds is being sold for human consumption [Klausner (l986)]; [Fowler et al. (l988:1-2/129-144)]; [Schneider (l989.a)]; Richards (l989)]; [Anderson (l989)]. The marketing of bGH is facing strong oposition from the industry, since resulting increases in productivity would most likely depress profit rates [6]. (See annex to ch. III).

II.ii.iv. Chemicals

II.ii.iv.i Commodity chemicals

Biotechnology has much to contribute to basic chemical industries but this is unlikely to materialize as long as petroleum prices remain at current levels. In contrast, much is going on concerning specialities (see below).

Most commodity chemicals can be manufactured biosynthetically (Table 4 provides some examples).

Table 4

Commodity chemicals: Examples of Alternative Bioprocesses

Product	Current (chemical) process	1987 US Market (in $ millions)	Bioprocess alternative
Acetic Acid	Oxidation of acetaldehyde	800	Acetobacter
Acetone	Oxidation of cumene	500	Clostridium
Butanol	Reduction of butanol	300	Clostridium
Ethanol	Hydration of ethylene	100	Saccharomyces

Source: [Consulting Resources Corporation (l989)]

Only if crude oil-based feedstock prices **tripled** would biomass feedstocks start making economic sense, though the huge sums of capital sunk in conventional petrochemical facilities would deter a rapid shift to bioprocess alternatives. But, of course, there is meanwhile plenty of room for improving the relative efficiency of these bioprocesses. Some firms are attempting to exploit this potential -- although prospects do not look too bright for the foreseeable future and hence not much money is being channelled into financing this type of R&D efforts.

The DBE Cetus, sponsored by National Distillers, has been working for over a decade on the development of micro-organisms and enzymes for a continuous fermentation process to produce ethanol. Scientists are studying the use of rDNA techniques to engineer new, custom made, enzymes that might allow dramatic improvements in known bioprocesses. Efforts are also taking place in the field of antibodies. Scripps Clinic & Research Foundation and the University of California have recently announced preliminary success in creating "catalytic antibodies" or "abzymes", whereby the antigen-binding property of antibodies and the chemical reaction-calalyzing function of enzymes are combined. Their commercial potential is being explored by DBE IGEN [Shamel and Chow (l989:682)].

II.ii.iv.ii. Specialty chemicals [7]

Specialty chemicals comprise amino acids, enzymes, vitamins, oils, aromatic compounds, biopolymers and dyes.

Enzymes and amino acids are the main products already on the specialty chemicals market, including the first genetically engineered laundry detergent lipase, marketed by leading enzyme producer Novo-Nordisk (it captured 15% of the Japanese market just two months after being introduced) [Laperrousaz (l989:57)] [8]. DBE Genencor, a Genentech subsidiary, and leader in the application of protein engineering technology to enzyme design, is also commercializing several proteases and lipases.

As in most other cases, engineered specialty chemicals compete, still rather tentatively, with products of chemical synthesis. The production of the former has the potential advantage of being simpler, less energy intensive and more specific (without so many byproducts). This is owed to the use of enzymes that perform the necessary conversions. Thus, vitamins, lipids, steroids and aromatic chemicals can be produced once the appropriate enzymes are identified and characterized and their genetic information cloned and expressed in micro-organisms. Chemical synthesis might eventually be entirely replaced by a biological process [USOTA (l984:195)].

Amino acids are used as animal feed and human food additives. They are also used as additives in cosmetics, antibiotics and herbicides. Their production is dominated by Japanese producers led by Ajinomoto (see section II.ii.v.). Although the specialty market accounts for a negligible proportion of world amino acid production by volume, it amounts to nearly one fifth of their sales value, which is around $2 billion.

Pharmaceutical-grade amino acids are produced by Abbott, Baxter Travenol and American Hospital Supply. All these companies are paying increasing attention to the biotechnological route.

Enzymes are proteins that act as very effective natural catalyzers. They have a wide range of actual and potential uses: for detergents (proteases), food additives (amylases and glucose isomerases), leather, pulp refining, and many products and processes [9]. Their world sales value is over $500 million [Shamel and Chow (l988:682)]. Novo-Nordisk and Gist-Brocades NV account for over two thirds of the world market. Other suppliers are CPC International, Clinton, Miles, Pfizer, Dawi Kasi, Alko, Finnish Sugar and Henkel. Because they are direct gene products, enzymes are appropriate for engineered improvement (yield increases of up to 500 per cent have been obtained in the lab) [USOTA (l984:195)]. DBEs Bethesda Research Laboratories, New England Biolabs and P-L Biochemicals and Boehringer Mannheim market engineered enzymes.

The impact of biotechnology on vitamin production is still very weak although, once again, it promises important potential costs savings, provided that efficient processes are developed (among other difficulties, not enough is known about vitamin bio-synthetic pathways). Efforts to replace some steps of vitamin C production with bioconversions have failed [USOTA (l984:l95)]. Genentech has developed a process to manufacture vitamin C that reduces to just one the first five steps of the current method.

II.ii.v. Food Additives

To say that biotechnologies have been used for food processing since time immemorial is a truism. But it is not easy to assess to what extent new methods are substituting for the traditional ones in this industry, save for the fact that it makes intensive use of enzymes whose production, in turn, increasingly relies on said methods (see section II.ii.iv).

There is a wide blurred area in this respect. And, unfortunately, the available literature is not of much help since most of it refers to the application of conventional biotechnology to food (and drinks) production and does not attempt to distinguish clearly between it and the new biotechnology [See, for example, [Antébi and Fishlock (l986:Ch. 13)] and [Hacking (l986:Ch. 7)].

The case of sweeteners perhaps best illustrates the impact that biotechnology is having (and will have) on established markets that are critical for LDCs. Per capita consumption in the US was 101.8 pounds for refined sugar and 26.6 for sugar substitutes in l970. The values were 62.6 and 89.8%, respectively, in l988 [US Department of Agriculture (l989)].

The introduction of high fructose corn syrup (HFCS), a sweetener from corn using immobilized enzymes had already seriously eroded traditional sugar markets by the early l980s, when aspartame entered the market in the mid-l980s.

By l988, fully 60% of the US per capita consumption of sweeteners consisted of sugar substitutes, with HFCS still remaining as the dominant substitute. The livelihood of an estimated 8 to 10 million people in the Third World is at stake [Ibid].

Let us now consider the case of cacao [10]. The new biotechnology threatens to undermine the comparative advantage of certain cocoa producing countries by making production independent of climatic and geographic conditions, and producing cacao butter substitutes. From the standpoint of importing DCs (a handful of which account for more than half of world chocolate and chocolate product imports) these alternatives are obviously very attractive.

Pennsylvania State University is presently conducting research in the molecular biology of a cocoa strain. This project, which is funded by the US Chocolate Manufacturers Association, aims at improving the yield and quality of cocoa plants through genetic engineering techniques. According to one source [Juma (l989:139-40)], the hybrid varieties may favour capital-intensive, large-farm cocoa producing countries like Brazil and Malaysia to the detriment of the African countries.

Laboratory production of cacao butter through tissue culture techniques is another path being followed by LECs. Such food industry giants as Nestlé and Hershey have teamed up with DBEs and universities (Hershey has agreements with DNA Plant Technology and with Cornell University) in this area, the interest of which lies in the fact that it would dissociate cacao butter production both from cocoa imports and from all land constraints, since cells could be grown in fermentation vats.

Finally, the all out replacement of cacao butter by modified inexpensive vegetable oils (eg. palm and soybean oils) is presently being explored by both Japanese and American interests. The Japanese food giant Ajinomoto has licensed a Tokyo University researcher's patented process involving the use of enzymes to produce a vegetable oil substitute. In the U.S., both Genencor and CPC are doing work along similar lines. Although the relative competitivity of cacao butter substitutes have yet to be determined, it is not impossible that they follow a trajectory analogous to that of sugar substitutes.

In 1973, Unilever isolated the basic properties of thaumatine, a natural sweetener derived from a Sudanese fruit. 10 years later the company succeeded in cloning it and had it expressed by Plant Genetic Systems in Ghent. Other companies working in this field are Beatrice Foods, through INGENE, and Monsanto, through DNA Plant Technology. The family of thaumatines has a sweetening power 5.000 times that of saccharose (compared with 300 for saccharin). None of these innovations has proven to be clearly competitive as yet, which obviously has limited their rate of diffusion (see section III.v).

Searle, today a division of Monsanto, has been producing aspartame by the chemical route at the lab scale since its discovery by one of the company's scientists in the UK in 1965. Introduced back in 1981 for tabletop and other uses, and in 1983 for use in carbonated beverages, it gained commercial importance in the US mass market only towards the mid-1980s, after the company succeeded in producing it by cloning a gene of polyaspartame. In 1984 Searle and Ajinomoto set up a joint subsidiary, Nutrasweet (a trade name for aspartame). Through it they still aggresively control most of the low-calorie sweeteners market, although a host of newcomers are trying to take advantage of expiring Nutrasweet-related patents (they have already expired in Europe and Canada and will do so in the US in 1992, where they protect 60 per cent of total sales). Today Nutrasweet commands a market of over $700 million with an extremely high profit margin (operating income in 1988 amounted to $330 million with sales worth $736 million) [Shapiro (1989)].

Aspartame began quickly displacing saccharin, for it has the advantage of lacking the metallic aftertaste of the latter (by 1978 it had gained about 70 per cent of the low-calorie market) [*Chemical Engineering* (1989:47)]. Saccharin consumption has remained stagnant over the last couple of decades. Since aspartame was introduced both the chemical and the biotechnological routes have been competing.

Aspartame competes with isoglucose which has become the second important sweetener in beverages (it has the disadvantage, though, that it is available only as a syrup). Other artificial sweeteners obtained by the chemical route, such as the L glucids, are already on the market--or approaching it.

Aspartame's most serious new contender appears to be Hoescht's acesulfame-K, authorised in the US market by the FDA in l988 for dry mixes. 200 times sweeter than sugar, it is so far being used as an ingredient in dry beverage mixes and chewing gum. It has the handicap of a slight afterstate. For this reason, Hoescht is trying to blend it with other sweeteners, a practice that is becoming increasingly diffused in Europe. When blended with aspartame, acesulfame-K tastes like sugar, tones down its afterstate and is about 30-40 per cent sweeter than either of the two.

The total US sweeteners market amounts to around $6.1 billion [*Chemical Engineering* (l989)].

Tissue culture-based vanilla production is taking place at lab scale [Rural Advancement Fund International (l987:35)]. If competitive methods are developed, this will threaten Third World exports valued at around $ 70 million [see section III.v) [11]. Similar developments are taking place with regard to grape and strawberry flavors.

In addition, plant tissue culture is used to develop new varieties of hardy, disease-resistant vanilla plants that could be grown outside their natural habitat and, therefore, in the DCs. A similar case is that of palm oil plants.

Because of its milk-clotting properties, rennet is an enzyme widely used in cheese production. Rennet cloning was first reported in Japan in l981. Later, DBEs Genex, Collaborative Research, Genencor and Celltech in the UK replicated the experiment (Collaborative Research holds a US patent). Engineered calf rennet was first commercialized in the US in the mid-l980s.

II.ii.vi. Minerals

As in the case of other applications, the boundaries between the use of new biotechnologies and that of more conventional ones are not altogether clear. In any case, as in all other industries engaged in taking advantage of bioprocesses, there is a potential profit to be made by introducing the new techniques, which is almost entirely untapped. Taking advantage of this potential would demand an amount of resources that is just not available, so that progress in this field is incipient and can be expected to proceed at a very slow rate.

Another reason for this expected slow rate has to do with sparse human resources. Most industrial experts in this field are chemical engineers, and know little about microbiological processes. These processes are studied mostly in universities and research institutes by scientists lacking engineering scale-up skills and related resources [Warhurst (l989:14)].

Advanced biotechnology is being used to overcome the high costs and technical shortcomings of known microbial processes [12]. Different plasmids of an uranium-resistant strain have been isolated, cloned and expressed in *E. Coli* at General Electric. The genes would code for substances that become attached to metals and destroy their toxicity. The same results have been achieved for iron at McGill University (Montreal). Plasmids of a strain that tolerates arsenic (present in many veins of gold) have also been isolated at Cape Town University [Antébi and Fishlock (l986)]. This may lead to dramatic yield increases while supressing production of highly poisonous sulfurous gases. Pilot industrial tests are being carried out.

Currently, 10% of the copper produced in the US is obtained using bacteria in either dump, heap or vat leaching. BC Research, a Canadian company, has developed a bacterial leaching process that can compete with smelting systems for veins rich in copper and, possibly, nickel and zinc as well. This process is reported to produce sulfur as a by-product and reduce costs by 28%. Scaling up efforts are being supported by a consortium of companies that includes BP Minerals and Somito Mining [Ibid].

Other alternatives, such as spraying bacteria directly into the mine, are still rendering very low yields (this route is being pursued by the Institute for Industrial Research and Standards in Dublin). Mineral companies like Chevron, Noranda (Quebec), Inco (in this case jointly with Biogen) are also working in this field. Engelhard Corp. has developed two systems for recovering metals by using fungus organisms in waste water. Kodak's scientists have isolated a bacteriuim from photographic emulsions that can extract silver from silver sulfide solutions [Ibid].

Apparently Advanced Mineral Technologies (Socorro, New Mexico) is the only DBE operating in mineral applications in the US. In Canada, there are two DBEs in this field, which pursue contrasting strategies. One of them has chosen to diversify into all areas of mineral processing and is doing well. The other chose to specialize in biotechnology applications for high value gold extraction and is on the verge of failure largely because of a lack of industrial processing skills [Warhurst (l989:15-16)].

II.iii. Trends in the Diffusion of Biotechnology

II.iii.i. General Assessment

A survey of OECD-based companies suggests that the 1990s will almost certainly witness the acquisition of biotechnological capabilities by increasing numbers of pharmaceutical, agri-industrial and, to a much lesser extent, food processing, and other types of companies [See OECD (l989:11)].

However, such efforts will continue to be made above all at the R&D stage. It is not so certain that technological capabilities will catch up any time soon with the acquisition of applied scientific skills at the enterprise level. Probably some 20 or 30 years at least will elapse before biotechnology becomes a widely utilized technology, affecting many industrial sectors.

Market forecasts must be treated with great care. There is a need to be extremely cautious in diffusion rates projections because it is much too early to even specify the assumptions such forecasts are based on. Estimations differ wildly [OECD (1988)]. At the aggregate level predictions for the year 2000 range from $9.000 to 100.000 billion. Mistaken (often self-seeking) forecasts on the speed of movement of scientific, technological and commercial frontiers abound. There are many examples of this [13]. Even at the product level forecasts have often proven to be irrealistic because those that produce the forecasts usually are the interested parties themselves [14].

As an example, the president of Agrigenetics has been quoted as having stated on agricultural applications that "new biological pest controls and hardier plant varieties would turn farm chemicals into museum pieces within a few decades". Ironically enough, Agrigenetics was later taken over by Lubrizol, a major chemical concern [Fowler et al. (l988:75].

Therefore, when looking forward, what matters most at this stage is the qualitative appraisal of possible diffusion trends and underlying assumptions which, in itself, represents quite a challenge. Another way of assessing potential markets is from the standpoint of needs: for example, 350 million people suffer amebiasis, more than 400 million people thachome, 100 million malaria, etc. [USOTA (l984)]. However, as the case of vaccines to be reviewed further on illustrates, biotechnology is unlikely to make a difference for these people.

Progress in some applications can be expected to pull progress in other applications as a result of spillovers affecting interindustry diffusion rates. Thus, for instance, US National Institutes of Health-funded research, aimed at applications in the field of medicine, is also expected to have an immediate impact on applications to agriculture, marine biology, the use of micro-organisms in waste management, and many other fields [USOTA (1989:16)].

One seemingly reasonable growth estimation is that of Consulting Resources (Lexington, MA). This firm forecasts that, overall, the US biotechnology industry will grow at an average rate of around 25% per year through the turn of the century, when total sales could reach $11 billion [*Chemicalweek* (l989.b)]. However, important macroeconomic impacts of biotechnology should not be expected before the second decade of the next century, if then [OECD (l989):14].

Undoubtly, biotechnology will strengthen trade reversals between DCs and LDCs, as the case of sugar substitutes clearly shows. The few biotechnology products already on the market are too expensive to reach LDC populations, beyond the fact that, by and large, they are aimed at DC-specific health problems. Finally, although dramatic increases in production efficiency may result from the use of biotechnology processes in a wide variety of industrial activities, there are still many engineering bottlenecks to be surmounted before such potential can be realized.

While diffusion of biotechnology products and processes is slowly beginning to gain momentum, the environment and the innovations themselves are changing permanently. In this uncertain environment, first comers, and even close followers, have little choice but to try to recover their sunk R&D investment in as short a time as possible and, hence, to charge exceedingly high prices, which makes reaching the mass market competitively rather problematic, no matter how intrinsically advantageous their products and processes may be.

High profit margins might be expected to induce the expansion of industrial capabilities and skills and thus sustain a rapid adoption process. However, isolated, unique products are unlikely to generate such a trend. The still questionable commercial feasibility of many applications raises a big question as to future diffusion rates. These are not likely to pick up unless greater advantage is taken of economies of scope and scale up-related bottlenecks are overcome.

As diffusion proceeds, the main thrust of the dominant natural trajectory of the industry may change. Thus, it may shift from diagnosis to therapeutics and prevention, from process to product innovation in agriculture-related applications and, eventually, as the basic techniques become increasingly routinized, towards food, basic chemicals, biomass and waste disposal.

Systemic (social, institutional, financial) innovations are critical for society to profit from the contributions of biotechnology. For instance, in the health care sector, the diffusion of biotechnology applications goes hand in hand with the need to automatize treatment, interpretation, transmission and research work and to adjust medical and financial practices [OECD (l989:14)].

II.iii.ii. Pharmaceuticals

The scientific frontier in biopharmacetucials has been moving somewhat ahead of expectations whereas the opposite has been true of the commercial frontier. This despite the fact that progress has taken place in technology, particularly in fermentation-related areas such as: (i) fermentation control systems; (ii) real time monitoring; (iii) analytic control systems; (iv) cell culture; (v) product separation and purification (which, together with dosage, account for a large proportion of final cost); (vi) scaling up; and, (vii) isolation and purification of biologic macro-molecules (peptides and proteins). Nonetheless, important technological challenges are still to be overcome (see section III.iii.ii.)

One industry source estimates that sales of biotechnology-based pharmaceuticals in the USA will reach $2.5 billion in l990 [PMA (l989)].

It is unlikely, however, that therapeutic genetics will be applied massively before the end of the century (among other things, the mechanisms of cellular transformation and genetic expression still require better understanding--see section III.ii.).

The fight against cancer and AIDS is not giving much hope for the immediate future. Likewise, the first new treatments for auto-immune disorders such as rheumatoid arthritis, diabetes and multiple slerosis which, together with cancer and AIDS, are drawing the most attention, are not likely to be available before the turn of the century. Dosage problems have entailed delays with regard to forecasts issued some years ago: the large molecules in protein and peptidic drugs cannot be ingested orally without being previously degraded. Similar problems exist via injection (see section III.ii.).

It is expected that novel delivery systems critical to the diffusion of biopharmaceuticals will enter the market within the next few years. Included amongst them are new oral forms, magnetic systems, transdermals, infusion pumps, ocular and nasal systems, bioerodible implants, liposomes, and aerosols. The market for these systems is forecast to reach $4.5 billion in the USA by the early l990s [Department of Commerce (l987:17-7)].

In Mab-based products some estimates put the US market at $6 billion towards the second half of the l990s, largely as a result of a rapid replacement of conventional techniques using polyclonal antibodies [15]. *In vitro* diagnostic tests are forecast to soon account for over 60 per cent of the total immunodiagnostics market, reaching $1.3 billion in sales in l992 (the Mabs themselves represent only some10/15% of that value). However, the other two components of the Mab market, *in vivo* diagnostics and, particularly, Mab-based therapeutics, are expected to reverse the importance of *in vivo* diagnostics toward the mid-l990s in their favour [Koenig (l989:5)].

As new products and applications develop, such as interleukin-2, colony stimulating factors and growth factors, worldwide consumption of peptides (60 per cent of which is used in human health case) is forecast to grow at 13 per cent per year, reaching $ 13.3 billion by l996 (including $5.9 billion in Europe and $2.2 billion in Japan) [Twersky and Rhoades (l989:9)].

In automation equipment, some product lines are expected to triple towards the mid-l990s as a result of a drive by biotechnology firms to more fully automate the entire sequencing process by adding more data capabilities and related equipment. In particular, the rate of growth of handling sales of automated instrumentation in the US (DNA and protein/peptide synthesizers and sequencers), may be close to 26 per cent over the next five years. The development of lower cost instruments may make items such as protein sequencers more affordable than at present [Gray (l989:12)].

As far as recombinant products are concerned, there are 23 basic product varieties at different stages of development in the US biotechnology pipeline, a good deal of which are likely to reach the market within the next 5 years [Sercovich and Leopold (forthcoming)].

The list of products in the pipeline includes, among others (indications are shown in parentheses): atrial natiuretic factor (blood pressure regulator); epidermal growth factor (wound healing); fibroblast growth factor (wound healing); granulocyte colony stimulating factor (leukemia and AIDS); gamma-interferon (hairy cell leukemia); interleukin-2 and 3 (various cancers and AIDS); macrophage colony stimulating factor (infectious diseases, cancer); superoxide dismutase (cardiac treatment and organ transplants); and tumor necrosis factor (antitumor and antiviral therapy)[16].

These products are being developed by alliances involving several dozen companies. On this basis, one likely scenario is that by l995, *cœteris paribus* , the US biopharmaceutical market may consist of a total of just over 30-odd products being offered by some 64 companies with full rights to--though not necessarily an equal share in--the resulting profits. This does not include an extremely wide range of critical input, service and equipment suppliers, which makes a profit squeeze even more likely and the bargaining equation even harder. The list of companies includes 20 large pharmaceutical multinationals, which are showing increasing interest and activity in biotechnology (see section on company strategies). [For further details at the company level, see Sercovich and Leopold (forthcoming)].

Certainly an overcrowded market seems a highly unviable scenario for most players. The weakest among them would be placed in an unbearable position. They are certainly not likely to wait until the last minute to do something about it (like getting out of the game before is too late). In fact, this swarming phenomenon, added to the still uncertain competitiveness of biotechnological products (see in section III.v.), makes the autonomous survival of many DBEs and the profitability of those that will stay in the market rather problematic (idem).

In an industry where an after-tax profit margin on sales of around 15 per cent is considered a must in order to finance R&D expenditures that account, on average, for around $100/120 million per product and 7/10 years from conception to commercialization, the swarming phenomenon in question makes a "reasonable" return for everybody concerned highly unlikely, even after allowing for the following facts: (i) some of these biologicals may prove to be blockbusters ie., products commanding a market of over $250 million per year (which is yet to be the case); (ii) biotechnology makes drug design more rational and should therefore allow for some cost reduction and (iii) the bargaining balance between those who share in the profits is normally highly uneven [For further elaboration on this, see Sercovich and Leopold (forthcoming)].

This appears to be a far cry from the "Schumpeterian Mark-I" upswing that some have anticipated based on the rise of large numbers of biotechnological **research** companies (see, for instance, [Kenney (l986.a)]. Leaving aside those that work as intermediate suppliers or that manage to find a comfortable niche market such as in delivery devices, many of these companies can probably only hope to become research boutiques or specialized R&D subcontractors, ie., something resembling a fixed research overhead from the point of view of the industry as a whole. Thus, they would turn out to be, at most, marginal players in the competitive arena [Sercovich and Leopold (forthcoming)].

Only dramatic quantum leaps in the relative competitiveness of biotechnology products and processes vis-à-vis established products and processes may smooth the impact of approaching growth traumas. But such leaps are not too likely in the near future, if only because many of the key players in the game are simultaneously those who would have the most to lose and the only ones with the required technological and financial muscle to push them forward [Ibid].

DBEs are becoming painfully aware that, in order to have their breakthroughs give rise to massively marketed pharmaceutical products, they need, among other things, to present them in the form of pills rather than injectable substances--which is something linked to serendipity and financial and industrial resources rather than to fundamental science skills. In fact, to do so, they may not have much alternative but to wed their technology with the old-line empirical skill of making synthetic chemicals. By themselves, DBEs just lack what it takes to handle commercially this likely marriage between genetic engineering and synthetic chemistry [Bylinsky (l988:159)].

II.iii.iii. Agriculture and animal husbandry

Efforts aimed at outlining the future of agricultural, particularly plant-related, biotechnology applications are even more tentative than in human health care. The R&D frontier is less advanced, more fraught with difficulties and considerably less well funded. Obstacles to cost-effective production remain to be surmounted. Regulatory and economic constraints are greater. And the public is not receptive. For these reasons (see next chapter), a time frame for market introduction can at best consist of informed guesswork, except in the case of a few products that seem to be quite close to market. In addition, save a few instances, there is little information available about potential market size.

If regulatory and economic criteria are met, bioengineered plants and microorganisms will begin to be commercially available in the early to mid-1990s. However, their rôle in agriculture is not likely to become truly significant until well into the next century. Herbicide- and pesticide- resistant plants and microbial pesticides are expected to play a supplemental albeit increasingly important rôle over the coming decades.

The first genetically engineered plant products will probably reach the market within the next 3 years. Commercialization is not too far off for many of the more important potential agricultural products such as genetically engineered crops, for which field trials are already underway.

For instance, Monsanto is field-testing genetically engineered cotton plants tolerant to the herbicide Roundup. Meanwhile, Agracetus is also field-testing genetically engineered cotton that is resistant to tobacco budworms and cotton bollworms. Joint field trials are planned by Calgene and Monsanto of genetically engineered virus-resistant potato plants. Pesticide and herbicide-resistant tobacco plants and insect-resistant tomato plants have also been tested and could come to market in the current decade [*Chemicalweek* (l989.c):31].

The engineering of herbicide resistance into crops has met with considerable success. Resistant hybrid lines may be introduced within 3 to 4 years once extended field trials are completed and numerous technological, engineering, economic, legal and regulatory issues have been dealt with [Botterman and Leemans (l988)].

Because of unresolved gaps in scientific understanding, plants in which desired traits are controlled by multiple genes will not be commercially available until well into the future.

Recombinant microbial biopesticides represent a potentially lucrative market, which could reach $8 billion worldwide ($2 billion in the US) by the turn of the century [Thayer (l989.b:11)]; [*Chemistry in Britain* (l989.b:772)]. The willingness of industry to invest in the development and production of engineered biopesticides depends to a large extent upon regulatory policies and practices.

Biopesticides using killed genetically engineered microorganisms appear to be the first marketable class of products, since lengthy regulatory procedures related to field release can be avoided; they may come into the market in the early l990s. [US Department of Commerce (l989):19-4]. The commercial time frame for products using recombinant living microorganisms remains less clear; one expert at the US Environmental Protection Agency puts it at 10 to 12 years, which would shed doubt upon the prospect of a multibillion dollar market for the year 2000 [Burrill (l988:184)].

To the extent that herbicide resistant cultivars are designed to be used in conjunction with chemical herbicides, the size of their market will be closely linked to that of the herbicide industry; in1987, worldwide herbicide sales were on the order of $7 billion, with the U.S. market alone totaling nearly $3 billion [Thayer (l989.b:11)]; [Goldbaum and Mackerron (l989:9)]

In plant biotechnology the rate of diffusion is largely controlled by major seed and chemical companies with vested interests in the markets concerned because substitute products are often involved. Company strategies therefore play as important a rôle in this case as they do in that of pharmaceuticals. In other fields, such as energy applications, possible conflicts of interest of this kind are placed much farther into the future.

While the first genetically engineered herbicide tolerant seeds will be on the market within the next few years, artificial seeds are expected to reach it well into the current decade. In agricultural applications a coexistence between biological pest control and the old chemicals and crop varieties that have been adapted to tolerate even more chemicals during a rather protracted period can be anticipated.

A two-stage diffusion process can be envisaged in this sector whereby agrichemicals will slowly be displaced [17]. This process would consist of:

(i) innovations geared to increase plants' herbicide-resistant attributes: first through herbicide resistant seeds and then through artifical seeds in which herbicide resistant attributes will be packaged with the herbicides themselves into non-reproducible seeds using new herbicide generations to the rate that the old ones have their patent validity expired; and,

(ii) innovations consisting of the introduction of live-microorganism biofungicides, bioherbicides, bioinsecticides and nitrogen fixation bioproducts whose timing of introduction is still uncertain, although expected to start by early next century [Doyle (1986:229)].

Diagnostic tests to detect diseases and virus in plants with the help of nucleic acid hybridation techniques are also expected to reach the market during the current decade.

Agricultural applications may begin growing at a faster rate than that of biotherapeuticals or diagnostics toward the close of the century [*Chemicalweek* (l989.b)].

In the area of animal husbandry, bGH is likely to be marketed starting this year, thus becoming the first product of agricultural biotechnology to be commercially available. However, a broad range of regulatory, public opinion and socio-economic factors make the prospect still somewhat uncertain (see next chapter). Initial market size is estimated at more or less $500 million per year [Richards (l989)].

BGH is perceived as a potentially precedent-setting case in the field of regulation and it has been provoking strong negative reaction on the part of certain intermediate and final consumer groups (see annex to chapter III). It remains to be seen whether in this case, as in others that impact farm economics and/or involve what is ultimately linked to food products, critics will succeed in creating significant barriers to commercialization.

In August 1989 the EEC rejected a plan for a 18 to 24 months moratorium on the use of bGH, but decided to put off a decision on wide scale commercialization [Dixon (1989:985)].

Transgenic farm animals with traits allowing for improved productive efficiency, disease resistance and product quality might be marketed by the end of the 1990s [US Department of Commerce (1989:19-3)].

In veterinary health care, it is anticipated that eventually all conventional vaccines will be replaced by recombinant vaccines, but the time frame appears uncertain. The market for these products could be substantial, as vaccines presently account for almost 25 per cent of an estimated $6.8 billion in worldwide sales in animal health care [Green (1989)].

II.iii.iv. Chemicals

The knowledge base in chemical applications is still relatively limited. For instance, the potential of enzymes to catalyze specific reactions is still largely unexplored. Natural enzymes are far from having been identified [Laperrousaz (1989)]. Most of the action in this field still remains at the lab scale. This does not mean, however, that said activity is not hectic (see below). Through genetic engineering and protein engineering, enzymes can be produced more effectively and in such a way as to render them more active, selective and stable vis-à-vis changes in temperature, pH, etc.

As pointed out further above, the reduction in petroleum prices has caused a slowing down of efforts devoted to commodity chemical product substitution; the respective rate of diffusion is therefore expected to be very low for what remains of the present century [OECD (1988:8)].

The relative sluggishness of developments in the specialty segment compared to pharmaceticals is due partly to the focusing of biotechnology funding on health-care. But perhaps more important is the fact that biotechnological processes do not yet show a distinct advantage over conventional processes while the amounts of R&D investment required to change this situation are substantial.

Because of high costs and still unsurmounted scientific uncertainties and technological bottlenecks, only around two per cent of the current total US market for specialty chemicals ($40 billion) is expected to be susceptible to penetration by new biotechnology-based products during the course of the 1990s [Shamel and Chow (1988:682)]. However, specialty chemicals are expected to begin growing faster than biotherapeuticals or diagnostics towards the turn of the century [*Chemicalweek* (1989.b)].

It is thought to be unlikely that the value of biotechnology-based chemical products and processes will surpass one per cent of the $200 billion overall

US chemical process industry before the start of the next century [Shamel and Chow (I989:682)].

Large chemical multinationals are slowly shifting their operations towards biotechnology. ICI, for instance, is investing $20 million through ICI biological products in a multipurpose biotechnological facility to produce novel biodegradable plastics, enzymes and forage (silage) preservation products, all specialties with high growth and profit potential. This way, ICI expects to recover some of the losses incurred in its commercially ill-fated single-cell protein animal feed supplement (trade-named Pruteen) by taking advantage of the experience and knowledge gained then, particularly in fermentation (Pruteen could not compete with soybean animal feed) [*Chemical and Engineering News* (I989.a)].

Monsanto alone devotes over $100 million annually to biotechnology R&D while DuPont is said to invest over 20 per cent of its total R&D budget of $1.4 billion in biotechnology-related research [Shamel and Chow (I988:681)]; [Weber (I989:81)].

II.iii.v. Food additives

Scientists are working with three-dimensional computer models of protein-like sweeteners to define the molecular basis of taste, including sweetness. This way, some molecules have already been produced that are up to 10.000 times sweeter than sugar. The paradox is that, although considerable resources are being spent in DCs to mimic the unusual attributes of sugar, there are still serious doubts that sugar substitutes are necessarily beneficial or warranted [Leary (I989:C9)] [18].

A wide variety of additional sweeteners will be reaching the market within the next few years [19]. All of them are, still unsuccessfully, attempting to emulate sugar's properties (taste, texture, heat stability, synergy with other sweeteners, bulking and shelf life) while avoiding its caloric content.

Among the new artificial sweeteners to enter the US market within the next few years (dozens are in development), the most significant are alitame (Pfizer) and sucralose (Tale & Lyle). Each expects approval for 15 uses, including baked goods, beverages and tabletop applications. Alitame is 2,000 times and sucralose 600 times sweeter than sugar. Their low caloric content plus the tiny amounts needed as compared with sugar explain their competitive edge, despite their more limited attributes [Leary (I989:C9)].

Thaumatin, isomalt (Subungsmittel GmbH) and L-sugar (Biospherics Inc), are still at the development stage inspite of good prospects and doubts remain about their potential competitiveness. Thaumatin, the most advanced of the lot, is expected to start marketing tests in I992.

II.iii.vi. Minerals

LDCs have a special stake in the development and diffusion of biotechnology's mining applications. It is in these countries where most of the new projects and unexplored mineralized zones are located.

Although, because of site-specific geological characteristics, no single process is expected to dominate on pure cost grounds, bacterial leaching apparently is an appropriate technique for LDCs' mineral deposits, which can, among others, broaden the choice of process routes for both mineral extraction and metal recovery [Warhurst (l984)].

In the future, vat or confined bacterial leaching systems may become a valid economic alternative to smelting for copper concentrates obtention. Pilot plant trials indicate that, at the energy costs prevailing during the mid-80s, bacterial leaching of copper concentrates may be carried out successfully at 60-70% of the cost of a similar smelting operation while allowing the economic recovery of associated precious metals like gold and silver. In addition, bacterial leaching can be used to solve such metallurgical problems as separation of lead from zinc concentrates; arsenopyrite from copper smelter feeds; and of pyrite from disseminated gold-bearing ore [Ibid].

Because most commercial use of bacterial leaching so far applies to DCs' ancient dumps of what was up until now considered waste, yields underate the potential of the technology as a result of the fact that these dumps provide an inadequate environment for microbial activity. Yields could be considerable higher in LDC environments, which are usually more hospitable than those of DCs [Ibid].

Because of the long lead times required to develop mining projects, early consideration should be paid to making use of the biotechnological route. Nonetheless, the diffusion of mineral applications of biotechnology can not be expected to gain momentum any time soon.

One industry source estimates that mineral applications of biotechnology may command a *potential* market of $ 5 billion by the turn of the century (*Chemicalweek.* (l989.c)].

Notes

1: The first rDNA product for clinical use in humans has been human insulin, approved in the US by the Food and Drugs Administration in 1982 (see Table I.1.). Genentech's scientists devised the rDNA methods and Eli Lilly subsequently developed and marketed the product as therapy for diabetics. For details on the categories of proteins being developed as human therapeutics and the respective technologies used to make them see [USOTA (1984) and (1987.a)].

2: Biotechnology has brought great stimulation to the peptide market. Peptides comprise compounds which are both genetically engineered (like insulin) and chemically synthesized (like cyclosporine). Worldwide consumption of peptides is estimated at $5.5 billion in 1988 ($2.7 billion in the US alone). Human health accounts for 60 per cent of the peptide market. Food applications, largely aspartame (see section on food additives further below), account for around 25 per cent. The remainder is mainly taken by agriculture (glyphosate) [Twersky and Rhoades (1989:9)].

3: Several of the products whose commercialization has already been authorized consist of the same type of protein marketed by different companies for the same therapeutic use (ie., they are perfect substitutes).

4: Applied Biosystems is the leader in this market segment. It competes, amongst others, with Du Pont, Swedish Pharmacia-LKB, Porton International (UK) and Millipon. Other companies, like Hewlett- Packard, are expected to enter the market soon [Gray (1989:12)].

5: One of the most recent scientific breakthroughs in plant biotechnology has been the development of a technique for using plants to grow Mabs thus substituting mouse cells as a growth medium, which are expensive and sometimes rejected by patients [Balkeslee, S. (1989) and (1990)]. Plants are also being made to produce peptides in greenhouse experiments [Sterling (1989)]. At the same time, efforts are being applied to create transgenic cows, mice and other animals which can produce large amounts of useful substances (such as blood-clotting factors) in their milk. At least 4 patents are pending in the US Patent Office in this field. DBEs Immunex in the US and Pharmaceutical Proteins in the UK are working in it. DBE Integrated Genetics is also seeking similar patents [*Business Week* (1989.c)]

6: While the timing of introduction is thus being delayed, among others in order to avoid a supply glut, consider the situation of Pakistan, a country that, with 3 and a half times as much pasture as Wisconsin (US' most productive dairy state) and one and a half as many dairy cows, produces 25 per cent as much milk. Because its cows are barely 15 per cent as efficient as Wisconsin's, Pakistan spends around $ 30 million importing milk every year [*The Economist* (1990:79)].

7: Specialty chemicals are conventionally defined as chemicals whose price exceeds 50¢/kg. Commodity chemicals are chemicals that sell for less than 50¢/kg.

8: Novo Industry A/S and Nordisk Gentofte A/S, both Danish companies, agreed to merge in 1988. Novo, the world's largest producer of industrial enzymes, accounts for half of total world supply. Enzymes accounted for one third of Novo's 1987 sales. The company is also the world's second largest insulin producer, accounting for 26.8% of the market (after E. Lilly, with 36.6%). Novo is building a plant to manufacture an engineered blood-clotting product, Factor VIIa, used in the treatment of hemophiliacs. It also has several neurological drugs in the pipeline, including one for epilepsy, three antidepressants, and three anti-anxiety medications [Morris (1989:29)].

9: The French concern Cellulose du Pin has been trying the biotechnological route for pulp refining semi-commercially in various plants with very encouraging results so far. The enzymes are provided by Sugar Finnish (which has a joint project with Cellulose du Pin in the context of the Eureka project). In the case of the Poix-Terron plant in Ardennes, specialized in recycled paper, productivity increased by 10-15 per cent compared with the conventional mechanical process. Substantial improvements in the quality of mechanical pulp for newspapers can also be obtained. It is expected that the paper industry might become the fourth largest industrial enzyme user, after the detergent, sweetener and cheese industries [Laperrousaz (I989:57)].

10: Cocoa is a plant. Cacao butter is a product derived from that plant. Historically, the production of cocoa has been confined to tropical regions, indeed to countries having very specific climatic and geographic conditions. Thus, when colonial powers began moving plant germplasm from one continent to another, cocoa, which originated in Brazil and Mexico, was introduced into a limited number of countries in West Africa, Southeast Asia and the Caribbean. The seven most important cocoa producing countries, namely: the Ivory Coast, Ghana, Brazil, Cameroon, Nigeria, Malaysia and Equador, presently represent some 80% of world production and supply the bulk of the $2 to $2.6 billion in cocoa bean exports. The four African countries of the group alone account for 55% of the world market. Given their non-diversified economic base and the pervasiveness of small-holding agrarian structures, these African countries are particularly dependent upon cocoa both for export generated revenues and for employment. In Ghana, for instance, over 20 per cent of the work force is engaged in cocoa production. References: [Kloppenburg (1988)]; [OECD (I989)]; [Juma (1989)];[Hobbelink (I988)]; [Christian (I989)]; [Pimentel et al. (I989)]; [Fowler et. al. (I988)].

11: Fully 98% of the world vanilla crop is produced by four countries (Madagascar, Reunion, the Comoros and Indonesia). Three quarters of total world output comes from Madagascar where 70.000 small farmers grow this labour intensive crop. US vanilla imports ($47 million in I985) account for 58 per cent of total world supply [ibid].

12: *Thiobacillus ferroxidans* the best known of mineral fed bacteria operates at an extremely slow pace and, to make things worse, it presents traces of arsenic or lead or too high a concentration of copper or zinc in the case of precious-metal extraction.

13: As recently as I986, Peter Drake, a prestigious investment analyst then with Kidder Peabody, predicted that Genentech would have twelve products approved by by FDA by I990 [Teitelman (I989:192)]. By the end of 1989 it had just three (insulin, human growth hormone and t-PA) and is unlikely to get more before the mid-90s).

14: For instance, tissue plasminogen activator (t-PA), Genentech's presumed blockbuster, was expected to command a market of around $1 billion. These expectations had to be lowered down to, in the best of cases, one fourth of that figure.

15: To the extent that this figure includes monoclonal antibodies that are to be used as delivery systems for therapeutics, there is some overlapping between this figure and that provided in the previous paragraph.

16: Some of these products can be put to use for different medical applications. For instance, no less than 65 product varieties are being developed in the US just regarding cancer (14 for lung cancer, 20 for colon cancer, 16 for breast cancer, 10 for prostate cancer and 11 for skin cancer, including malignant melanoma). At the same time, there are 14 drug varieties focused on AIDS or HIV-related illnesses while 12 vaccine varieties are been tested for hepatitis B, malaria and HIV-AIDS [PMA (I989)].

17: This displacement has already started. For instance, Ciba-Geigy, although having the technology to produce straightforward herbicide-resistant crops, is beginning to pay increasing attention to insect and drought-resistant crops [*Chemistry in Britain* (I989.a:121)]. Beyond the "normal" damaging impact of chemical pesticides on human and animal health, pesticide production-related accidents, like that of U. Carbide in Bophal, that killed 2000 people and injured another 20.000, do little to offset their disrepute.

18: "There is nothing out there that can successfully replace sugar. Sugar has a lot of functional properties in food other than sweetness and no one has been able to duplicate all of them" [Clysdesdale (I989)]. The growing use of no-calorie and low-calorie sweeteners has not stopped obesity from increasing and there are no studies showing that lower or no-calorie sweeteners are effective as long-term weight loss aids [Jacobson, M. (I989)]. Likewise, food companies are effective as long-term weight loss aids [Jacobson, M. (I989)]. Likewise, food companies have been trying for years to convince people about the anti-cholesterol virtues of oat bran cereals. However, a study published in a January I990 of the New England Journal of Medicine suggests that these claims are unwarranted. The more people consume these "magic bullet" products, the more they indulge in consuming high calorie products. The case of low calorie sweeteners is entirely analogous. Surely, the key lies in overall diet and life-style rather than in "saviour" products.

19: "When you read the literature and talk to people at meetings, it seems that about every major food company in the US has someone doing sweetener research" [Keeney (I989)]. For instance, one of the largest world consumers, Coca Cola, has already patented its own low-calorie sweetener, which is still in early stages of development [Shapiro (I989)].

III. Factors Affecting the Timing of Introduction and the Rate of Diffusion of Biotechnology

III.i. Introduction

This chapter examines different factors that affect the timing of introduction and pace of diffusion of biotechnologies. The highly intricate interactions among these factors, over and above their individual complexities, do not make the task any easier. No simple and sharp distinction can be made between retardatory and accelerating factors, for some of them may act both ways according to circumstances and industries. However, on balance, retardatory forces appear to be prevailing so far making the actual rate of product introduction and diffusion lag behind the potential rate.

As we shall see below, public opinion is one of the forces with a dual impact. In agricultural applications it appears to be slowing down the timing of introduction, while in pharmaceuticals it accelerates it.

Likewise, companies under intense rivalry are often led to speed up the pre-introductory process so as to reach the market first. But this is not always the case. It depends on the type of company. Thus, for example, agrichemical enterprises are in no rush whatsoever to speed up the substitution of biotechnological inputs for what amounts to a profitable established market for agrichemicals.

Advances in the knowledge base are widely taken as being one of the main forces accounting for the development of biotechnology. However, at the same time, important gaps in scientific understanding remain and, more to the point, engineering knowledge is lagging. As a consequence it is proving rather difficult to reach the market with competitive products.

The relative lack of competitiveness of biotechnology products (even accounting for differences in quality as compared to conventional products) is one of the forces most clearly slowing down the rate of diffusion. This, in turn, has a lot to do with the existence of entry deterring barriers, which have not received enough attention so far. Scaling up problems, legal dispute over patents, skills shortages, and other factors are among such barriers [1]. Finally, regulation contributes to long lead times and heavy development expenses.

The existence of an unusual swarming phenomenon at the R&D stage, the slowing down factors just mentioned, long lead times, and relatively adverse conditions in capital markets (ie., increasing reluctance to support "magic bullet"-related business plans), are creating conditions of uncertainty likely to keep the rate of product development slow. DBEs' high financial burn rates and low survival rates are another clear expression of these difficult circumstances [Sercovich and Leopold (forthcoming)].

The sparsity of managerial, organizational, institutional and social innovations also works as as a retardatory factor in biotechnology diffusion. The current crisis of the US national health system referred to below is an example of the need for accomodation at those levels.

The availability of such skills as the ability to manage multidisciplinary R&D and take prompt advantage of synergies and cross-fertilization in scientific and technical knowledge is still another important dimension bearing upon diffusion rates, among other things, by facilitating or deterring the exploitation of spin-off potentials.

However, the rapid rhythm of scientific and technological progress in biotechnology can bring surprises by giving rise to breakthroughs that may radically change this situation at any time. Equally important, there is already in motion a very dynamic process of follow-up secondary innovations. Finally, changes in relative prices as a result of unexpected events may also place biotechnology processes and products at the centre of the competitive stage.

Biotechnology has given rise to some (not always unbiased) views that tend to confuse science with technology and to understate the distance between a scientific discovery and an economically profitable technical application.

For instance, one comes across statements like this: "One important characteristic of biotechnology is the very short lead time from discovery to application. A laboratory finding can, in many cases, lead to a path of product development almost immediately after the finding is published" [Johnston and Edwards (l987):7]. Not coincidentally, one of the writers of this sweeping statement (Johnston), is a venture capitalist. This sort of view has pervaded the writings of many authors (for an exception, see [Teitelman (l989)]. Although it is true that the new biotechnology has often brought about a compression of the different stages that go from basic scientific discoveries to actual applications, exaggerating the existence of short-cuts and quick fixes pays lip service to the interests of LDCs contemplating their entry into the industry [Sercovich and Leopold (forthcoming)].

The case of vaccines illustrates other obstacles to diffusion. Science push forces do not appear to work in this field. Obstacles to biotechnology introduction and diffusion (involving rendering products accessible to those who need them most dramatically, ie., LDC children) have little to do with limitations in the scientific base [2]. The problem of the relative lack of private interest in this field apparently lies, rather, on market failure. While "increased competition" is prescribed as the best way to go about promoting that interest, complaints are voiced at the same time, and by the same sources, about the fact that United Nations outfits promote "too much" price competition through their tenders to supply LDC needs. See [US Department of Commerce (l986:17-3)] and [(l988:18-3)]. See also [Neyret (l989:28)] [3].

For existent vaccines, LDCs have access at affordable prices only in those cases where investments have been fully amortized and from a few "well disposed", usually non-US, suppliers that welcome large orders-- channeled by WHO and UNICEF--when their domestic market is relatively narrow and they have the chance to reap substantial scale economies (ie., when the market consists of 40 million people or more) [Robbins and Freeman (l989)]. (For further discussion on this, see sections III.iii., III.v. and Chapter IV.).

III.ii. Scientific, technological and engineering bottlenecks and uncertainties

"Life by its very nature is resistant to simplification, whether on the level of single cells or ecological systems or human systems" [Dyson (l988: 95)]. The trajectory of the new biotechnology fully backs this assertion: every discovery seems only to unravel ever more complex leads. "No paradox, no progress" runs Bohr's dictum.

Important dissenting voices argue against apparently established scientific truths, as that holding that HIV-1 is the cause of AIDS, or the somatic mutation thesis, according to which damage to DNA is the primary event in carcinogenesis [Duesberg (1988:514)]; [Rubin (l980:999)].

Some basic questions about cancer (as well as about many other devastating contemporary diseases) still remain unanswered, such as whether it is a single disease or a complex of diseases; whether it is triggered by a common switch or by a multiple one; and whether the answer lies in the genome, in some still elusive pattern of oncogenes or in some higher level of organization [Teitelman (l989:204); Angier (1988)].

The same is true about the whole family of so-called auto-immune disorders. A properly working immune system distinguishes foreign matter from the body's own tissue. Scientists do not know yet why this fails to occur in some cases [Pollack (l990)].

Likewise, important gaps in knowledge are reported on protein structure and function, protein engineering, the rôle of natural chemical modifications of proteins in protein stability and function, and development of novel delivery systems for protein drugs [4].

Also, the basic science base in the plant sciences is regarded as seriously deficient [USOTA (1988:16)] [5].

Much premature excitement was created in the early days of biotechnology by daring scientific theories and promises of magic bullets and amazingly quick advances in immunotherapy that, when intended to be translated into technologies, resulted in disappointment and the unfolding of unsuspected complexities and contingencies [Teitelman (l989:9)]; Judson (l979):637].

The so-called "interferon crusade" story provides a good illustration [Teitelman: ch. 3; Panem (l984)], later to be reproduced in connection with interleukin-2 [6].

Clearly, this type of "hype" appears to be rather pervasive across scientific disciplines. The most recent case is that of the apparently premature reporting of the discovery of "cold fusion" by Martin Fleischmann and B. Stanley Pons. However, no instances can be found of these kinds of excitement having led to raising so much venture capital at such a steady rate over so long as in biotechnology.

Despite its spectacular rhythm of progress, the scientific knowledge base is still just not able to account satisfactorily for the complexities of molecular interactions within the human body. Not long ago, scientists had it that the body produced just one interferon molecule to fight infections. The number has now gone up to 19. Scientists can make molecules; but they do not yet understand well enough what to do with them [Bylinsky (l988):15)].

Genetically engineered products such as interferon, interleukin, growth hormones and human insulin are destroyed in the stomach if unprotected. The large molecules that form protein and peptidic drugs cannot be ingested orally without having been previously degraded, so that the only delivery route left is injection, which limits the market. The development of polymers and liposomes is expected to aid in transporting the active ingredients to specific sites where they can be effective. This will eventually lead to the fusion of genetic engineering with synthetic chemistry, or even the "co-opting" of the former by the latter, which happens to be the turf of pharmaceutical LECs (for further details, see section III.v.).

The US National Institutes of Health-NIH decided to begin accepting proposals for the first genetic experiments on humans in l985--on the grounds that scientists had learned enough about altering genes. However, the first authorized **testing** of modified human cells was to be performed by Genetic Therapy Inc. only by end-**1989** in cooperation with NIH scientists in an experiment where interleukin-2 was to be used as a catalyser. Important gaps in scientific understanding make progress in this area slow: since the basic Cohen-Boyer process patent, already a decade has elapsed even before authorized genetic tests on humans are to take place [*Business Week* (l989)]; [Nicolson (l989)]. Obviously, such gaps also affect the setting up of regulatory standards, which does not leave much alternative to protracted lead times (on this, see section III.iv.iii).

There are also cases of disappointment at the product level. For instance, PEG-SOD, an enzyme that helps reduce tissue damage in transplant operations, is proving less effective than anticipated [Hammonds (l989:72)].

Among traits which are poorly known in plant agriculture applications are stress and disease resistance and symbiotic microbe interactions. Understanding of gene expression is also insufficient [7].

The use of rDNA techniques to introduce disease resistance into plants has been retarded by an inadequate comprehension of the mechanisms of pathogenicity and resistance. [Brown et al. (l987:133)]. In the area of multiple gene transplants, the combination of scientific and technological obstacles makes it unlikely that traits obtained by such transfers will be engineered until well into the future [8].

Although great progress (greater than anticipated) has taken place in plant genetics since l982, important bottlenecks remain in areas such as: (i) genetic transcription; (ii) translocation; (iii) gene production; (iv) gene promotors; (v) tissue genetic regulation and development; and (vi) genetic induction.

Progress has also been made at a faster rate than expected in the use of microorganisms other than *E. Coli* as vectors of genetic expression. A similar case concerns new applications of *in vitro* gene amplification techniques. However, genetically modified microorganisms pose more uncertainty than their plant counterparts. It has yet to be proven that this uncertainty is susceptible to scientific evaluation and control [Godown (1989:1096)].

The genetic engineering of farm animals is hampered by significant technological difficulties that include the introducing of genes into ova, the successful implant of these ova into surrogate mothers, the bringing to term of resulting embryos, the demonstration that engineered traits are stable and heritable and the regulation of a cloned gene's expression in its host. These bottlenecks, combined with the timeframe linked to the gestation period, sexual maturation, and breeding cycles of large animals, mean that, all other obstacles notwithstanding, the commercialization of transgenic cattle, sheep and pigs is is not likely in the immediate future [Van Brunt (l988:1149-54)].

In the area of animal health care (hormones, vaccines, therapeuticals) scientific and technological bottlenecks are not too unlike those encountered in human health care. In the case of bGH, which can now be produced on an industrial scale, such bottlenecks have obviously been overcome. There is, however, room for improvement in the methods of administering the hormone, which presently is injected into the animal.

DCs still lack satisfactory risk assessment of biotechnology products. Inadequate risk assessment procedures hinder realization of field tests. Biotechnology might provide diagnosis of animal diseases, but providing cures is still far in the future [OECD (l988)].

In the case of mineral applications, as already pointed out in the previous chapter, serious scientific and technical problems still remain. Methods to cultivate bacteria on a solid feedstock (cultivation in suspension), raise yields, get rid of undesirable by-products, and serious environmental hazards are among them.

III.iii. Company strategy

Company strategy affects, and is in turn affected by, the complex set of forces that shape the development of the industry. According to type of enterprise, the nature of uncertainties and constraints that impinge upon strategy may vary considerably.

Thus, for instance, most DBEs active in the health care field proclaim their intention to become fully integrated pharmaceutical companies. However, except in the case of a firm like Genentech, these ambitions are a long shot. DBEs have to cope with a very volatile environment regarding things such as how their products will fare in the market, access to finance and strength of their patent position. This makes their potential entry very tentative, even in those (very frequent) cases were they get LECs' assistance for manufacturing and/or distribution and/or marketing.

Let us examine an example. DBE Liposome Technologies developed a modified agglutination test and then had Cooper Laboratories take care of marketing through a joint-venture agreement. Liposome is using the joint-venture to test the market for the new assays. Due to competition in the field (from conventional assays and from the newer ones based on liposomes) there is doubt about the success of any new product in the market. The main point about these first products is to establish the potential of the technology in order to make the companies more attractive to the investment community [*Bio/Technology* (l983.a)]

In mutual partnerships both DBEs and LECs have valuable assets to offer. The former provide their ability to leverage knowledge from universities; to hire university faculty on part-time basis; and, to motivate contributions of scientists-entrepreneurs through stock ownership and other economic incentives. LECs contribute their R&D financing muscle; regulation-related experience and resources; scaleup capacity; established marketing networks and diversity of product lines that make it possible to reap economies of scope. DBEs are increasingly relying on LECs to finance their research activity and, often, the price of this support is relinquishing control of their scientific and technological developments.

The existence in the US of an important already established market for specialized intermediate inputs (including reagents, services and instruments) where economies of scale are not critical, is another factor favouring the entry of a large numbers of DBEs.

Chemical and drug LECs enjoy a certain discretionary ability to pursue given routes of biotechnological development rather than others. Large agrichemical and pharmaceutical suppliers are handling biotechnology with great caution. Nonetheless, they are definitely entering it. Indeed, this involves embarking upon an entirely new route with high risks and heavy tradeoffs in respect to the chemical route. But, although LECs can affect decisively the timing of introduction and pace of diffusion of biotechnologies, they cannot suppress them, even assuming they wanted to, which is not necessarily the case. Among other things, a good deal of their current patents are expiring so that profit margins are inevitably going to suffer. Thus, although the intrinsic potential superiority of the biotechnological route remains to be shown, LECs are definitely open to the prospect of using it to recreate their weakening quasi-monopoly power.

The 1970s have witnessed the birth of industrial applications of biotechnology. During the 1980s LECs have cautiously followed events, becoming increasingly involved and thus getting ready to fully enter the field. During the 1990s they are likely to impress their particular mark upon future developments.

Although in both agrichemicals and conventional pharmaceuticals LECs confront diminishing quasi-monopoly power, there is still a long way to go before their products become unprofitable--leaving aside the fact that the chemical route is still far from having exhausted its innovative potential. As long as this remains so, LECs that have already taken steps to master the new biotechnologies are not anxious to cut their profits by prematurely releasing competitive products. Many of the new products may not work, or may not work adequately, or may create new problems for which a response is not yet available [Fowler (l988:72-93)]. The dificulty of replacing existing products is illustrated by the debate around Hybritech in the diagnostics field [*Bio/Technology* (l983.b); [Teitelman (l989)].

Nevertheless, major biotechnology-related industrial restructuring developments are in the works. One example is the dramatic current merger and takeover rush amounting to tens of billions of dollars and involving virtually all the world pharmaceutical majors [Sercovich and Leopold (forthcoming)]. The farm input industry provides another example. By the mid-1970s there were in the US some 30 companies engaged in pesticide development; now there are just a dozen, of which only one half may survive. So far it is cheaper to adapt the plant to the chemical than vice versa. As already mentioned, biotechnology is being used to extend the life cycle of existing agrichemicals (in some cases, with substantial expected increases in sales) [Ibid].

Another way in which company strategy is affecting the rate of diffusion of biotechnologies is through pricing policies. For instance, new bio-pharmaceuticals (as well as diagnostic kits) are coming to market at very high relative prices. In an extremely uncertain environment, the companies involved need to recover their R&D expenses as quickly as possible [9]. Once they have eventually done so, and if competition so requires, they may be able to price products at marginal costs and hence start a rather quick market development when price and income elasticities of demand are better known.

Industry-specific characteristics affect the pattern of diffusion of biotechnology applications. Two important variables in this respect are unit product value and R&D thresholds and payback periods. Thus, company strategy towards biotechnology, and with it, diffusion across industries, has to do with sector-specific business strategies (like that geared to keep given market share and profitability). Food companies, for instance, tend to focus on marketing strategies in markets where they control a good share of the supply. This contrasts with pharmaceutical companies, which are relatively more focused on new product development. This partly explains the higher involvement by the latter in biotechnology [OECD (l988)].

During the current, incipient stage, the diffusion of biotechnology among user industries is strongly dependent upon technical change **in the enabling technologies**, which is driven largely by DBEs [10]. This is, therefore, a science-led stage.

At a later point, once such innovations become standarized and routinized, user industries will themselves become increasingly involved in the innovation process as affected by their own profitability. The industry will thus enter its "market-driven" stage. This stage may begin towards the turn of the century.

Whether firms decide to enter biotechnology R&D or not depends on several factors, including their: (i) product mix (firms involved in antibiotics, beer, cheese and amino acids are relatively more prone to get involved since they are already familiarized with biotechnology); (ii) previous technological trajectory and skills (acquaintance with traditional biotechnology is highly correlated with involvement with the new); (iii) range of R&D capabilities; and (iv) attitudes towards innovation. User industries (or countries) may make better or worse use of their accumulated experience in order to take advantage of headstarts in biotechnology.

Because of increasingly complex, time consuming and costly R&D, in-house R&D is being discouraged, while collaboration to cut R&D costs, share expertise and speed development of innovative products is being encouraged [11]. Beyond the current wave of consolidations referred to above, this is translated into a dramatic development of strategic partnerships.

Demand for R&D funds is bringing about consolidation in industry in the form of mergers and acquisitions, especially involving smaller specialty manufacturers such as DBEs. Related to this, the focus of R&D efforts in the pharmaceutical industry is expected to shift from infectious diseases to chronic and degenerative diseases (that affect the most rapidly growing segment of OECD population, ie., those over 60 years old), as well as from basic to applied research.

It is interesting for illustrative purposes to take a look at an example of companies' acquisition strategies.

In the hepatitis B vaccine field alone, there are at least 14 players, in the North American market. This has led to some bitter takeover battles among them (in which cash-rich European concerns are key actors) [12].

One of these battles has recently taken place between the Swiss multinational Ciba-Geigy (in a joint venture with US DBE Chiron) and French serum maker Institute Mérieux (50.5% owned by Rhône Poulenc) for the acquisition of Connaught BioSciences, Canada's only large, world class biotechnology company active in the vaccine market. This example clearly illustrates the abrasive strategy pursued by the players in order to entice the takeover target, other interested parties and the Canadian government to agree to the acquisition at almost any cost, given the critical strategic importance of the move in order to gain a privileged position in the North American market[13].

Connaught itself was certainly not an unwilling takeover target. In June I989 its CEO told shareholders at the annual meeting that the company could not reach the critical mass required to compete in the global vaccine market alone and needed to merge with another vaccine company to survive.

But, then, the difficulties cropped up. To begin with, Investment Canada, the agency in charge of assessing takeovers of Canadian companies by foreign concerns, reached its first adverse net-benefit decision about a publicly traded company in its 4 years history. At the same time, a local group headed by scientist Robert Church attempted to generate a local alternative to a foreign takeover. Finally, the University of Toronto claimed that the transfer of control to a non-Canadian concern would violate the terms of a I972 agreement between the university and the Canadian government (the university, where artificial insulin was originated, founded the company in 1917; it sold it in I972 to the Federal government which, in turn, privatized it).

In addition, Mérieux faced regulatory hurdles in the US, where the Federal Trade Commission feared Connaught's takeover would hurt domestic vaccine makers. The foreign contenders managed to lift all these obstacles one by one, and to proceed with a takeover which was "regretfully" approved by the Canadian government.

To begin with, Mr. Church accepted to become a member of Ciba-Geigy's advisory board in case the Swiss company succeeded. Then, both contenders made research funding offers that induced the University of Toronto to reach an out-of-court settlement. In addition, both companies pledged to increase the transfer of technology, R&D, production and employment in Canada, thus doing away with the initial negative net-benefit assessment made by Investment Canada [14]. Finally, Mérieux managed to persuade the US FTC to lift its objections. All that remained was the competition on the actual amount offered to Connaught as takeover bid. Connaught's shares were valued at C$25 per unit (or a total of C$643 million) by Ciba-Geigy in mid-September. The final value with which Mérieux won the bid was C$37 per share, or a total value of C$943.5 million, that is, an increase of almost 50 per cent on the original bid. These events took place at a hectic pace between September and December I989.

Many of the companies that are getting involved in biotechnology are not "high-tech". Therefore, they cannot be expected to make a rapid transition . Thus for instance, average R&D intensity in chemicals is 4.1%, in food and beverages 0.9 per cent and in fuels 0.8 per cent as against 7.8 in drugs [*Business Week* (I989.f:139)].

User industry R&D intensity is a useful parameter to take into account when tackling the question of diffusion. The building up of "savoir faire maison" is going to take long in most biotechnology user industries, while the basic techniques are routinized and intermediate supplier networks developed. Compared with these prospects in most potential user companies, a large number of pharmaceutical firms are already spending between 25 and 40% of their R&D budgets in biotechnology (both old and new) [USOTA (l988.b)]. This percentage is much lower in agroindustry, although it is expected to grow at least until the mid-1990s [OECD (l989)].

Company-financed R&D in universities is 4 to 5 times greater in biotechnology than in other fields. Nearly half of biotechnology companies support university-based research [USOTA (l988.b)]. But now something appears to be changing: few companies are planning to invest large sums over long periods for **undirected** research, as was done in the early 1980s by Monsanto at Washington University (this strategy is now being taken over by foreign companies like Shiseido, with its $85 million agreement with the Harvard Medical School) [Weisman (l989)] [15]. An increasing number of cooperative arrangements represent consulting and contract research rather than long-term partnerships. One of the effects of this is increasing levels of secrecy in universities. Another is the emergence of shifts in the direction of the university research agenda toward more applied and commercially relevant projects [USOTA (l988.b:6)]. In conjunction, these effects can be expected to have an unfavourable impact on LDCs.

In the same way that LECs are putting money in universities, some universities are investing in DBEs, that is, becoming venture capitalists. One example is DBE Seragen, which works in the cancer field and which, although it is still very far from the market, has already received $60 million from its main shareholder, Boston University. The university is approaching its limit as a financier, after having committed nearly one-third of its endowment to the venture, thus getting involved in a "big gamble- high risk" situation (as in so many other cases, product development has been slower and more costly than anticipated). Currently, Boston University is in negotiations with potential partners, including Sandoz Pharmaceuticals, to stop a cash-flow hemorrhage of about $11 million per year [*Business Week* (l989.d:31) and (l990:32)].

The science-push biotechnology hype has been much closer to the realm of scientific possibility than to that of engineering feasibility, being even further removed from the realm of economic profitability. This hierarchy will have to be turned upon its head before biotechnology becomes widely diffused and its products massively marketed.

After the premium prices paid for DBEs like Hybritech (Elli Lilly) and Genetic Systems (Bristol-Myers), LECs' strategies have become more subtle. They do not have to engage in such outright commitments of resources anymore: DBEs' access to financial resources has become very difficult after the crash of l987; tax advantages for R&D Limited Partnerships (RDLP) have been withdrawn, and risks associated with biotechnology investment have gone up. These events are forcing many DBEs to seek funding from LECs at a price that is sometimes tantamount to the resignation of autonomy and hope for vertical integration that inspired their initial moves. Strategic partnering deals have thus acquired a definite importance in biotechnology as one of the main traits of market organization (see, for instance, the case of Nova in [Teitelman (l989:195/6)]. But, interestingly enough, it is often the very fact that DBEs are involved in such closely knit networks of alliances and mutual commitments that best deters their being taken over.

III.iv. Barriers to entry and threshold factors

III.iv.i. Introduction

Because of a somewhat loose use of the concept of "entry" into biotechnology in the literature, let us first of all distinguish between:

(i) entry into R&D, that is, **production of R&D services** (which is what most DBEs are about, working largely under contract); and,

(ii) competitive entry into production, marketing and distribution.

Entry into biotechnology R&D does not necessarily have much to do with such mundane things as costs, profitability, scale-up and markets. Basically, all that is required is a good group of high calibre scientists and an assured budget. But to enter into production, marketing and distribution competitively is quite something else.

The latter is a much more uncertain and ambitious proposition. This is so, among other things, because of:

(i) the paucity of off-the-shelf technological and manufacturing solutions to scientific problems;

(ii) the need to cope with environmental issues; and,

(iii) the presence of LECs with important economies of scale and scope, based on established products and processes, that are already preempting the new scientific and technological frontier by themselves (as they are increasingly inclined to do) and/or through third parties, like universities or DBEs (for an illustrative example involving Genetic Systems and Abbott in connection with AIDS tests, see [Teiltelman (l989):l7l]).

The allegedly relatively low barriers to entry into biotechnology is a point often referred to in the literature (see, for instance, [Rukstad (l987)]. Surely, save for a very limited number of biotechnological products, this refers only to the first type of entry, ie., entry into R&D. The trouble is that this often is **not** made explicit, which may mislead potential new entrants, including LDC firms. The passage from the lab to the industrial plant is far from trivial and there is little science can do about it, despite the "practical" nature of gene cut and paste engineering.

The relative weight of specific entry barriers in biotechnology differs across sectors. And within each sector, particularly because we are dealing with an emerging industry, such weight tends to change over time. Put another way, barriers to entry evolve with the stage of development of the applications.

While bottlenecks in scaling up and product design are exerting a decisive influence as an entry barrier in bio-pharmaceuticals, in agricultural applications regulation and public opinion presently are among the key entry barriers in the OECD countries--a situation that may change as regulatory uncertainties and public malaise are overcome and as agricultural biotechnology itself moves beyond the R&D phase.

According to conventional wisdom, opportunities for small companies tend to be greatest in the earliest stages of the product cycle, when scale economies are relatively unimportant, market shares volatile and rates of entry and failure high. At this stage, successful entry largely depends on scientific and technological capabilities. As technologies mature, scale and efficiency in production become more important and opportunities for small companies fewer [Perez and Soete (1989)] [16].

This is the conventional wisdom, the "stylized facts". However, a number of caveats have to be mentioned. First of all, the independent rôle of institutional, social and managerial aspects has to be taken into account. [Abramovitz (1989)] has made this clear when accounting for the gap between actual and potential realization of economic progress.

In the most advanced applications of biotech ie., bio-pharmaceuticals, engineering and manufacturing excellence began very early on to play an important rôle in the definition of successful entry. Even in the case of entirely new products, cost competitiveness as compared to existing alternatives are not of secondary importance. Without the rapid acquisition of effective scaling up capabilities and had their products not reached the necessary standards, the few **manufacturing** DBEs which have managed to stay in the market so far would not have succeeded --in which case LECs would have taken their place, as has often been the case.

With the progressive diffusion of the basic biotechniques, entry barriers are becoming increasingly application-specific and resembling those of the industries concerned. Thus, as the biotechnology industry matures, we witness an increasing differentiation of barriers to entry according to user industry. It makes less and less sense to refer to biotechnology- related entry barriers without specifying what industrial sector of application is being referred to.

This is another important caveat with regard to the "stylized facts", since the importance of the scientific base of departure is relativized downstream by the engineering, manufacturing, marketing, regulation, etc. requirements of the specific sector of application concerned, with its own standards, routines and practices, which may or may not be challenged.

"Entry" is commonly used with reference to individual firms. However, for a generic technology-based, emerging industry, it may also refer to a whole set of interacting institutions. This raises the question of the often neglected systemic aspects of entry. One of the keys to DBEs' survival (and one of the reasons why they are less likely to prosper in LDCs) is their close-knit relationship with LECs. To this, one should add the availability in the US of well-developed and organized venture capital markets and the favors they receive from the state through subsidized (tax exempted) schemes such as RDLP and tax treatment of patent royalty income [Doyle (l986:86]; [Saxonhouse (l986:34)].

Two stages can be distinguished in the typical relationships between DBEs and LECs. In the first, the R&D stage, LECs supply financing in exchange for research results. In the second, the production/marketing/distribution stage, LECs supply skills in exchange for rights to exploit DBEs' patents and know-how. More often than not DBEs have been founded by university-based scientists-entrepreneurs in association with venture capitalists. Later on they have often resorted to public IPOs ("Initial Public Offerings" on the stock exchange), forming joint-ventures and RDLPs. Some have been taken over by LECs, others have gone bankrupt and others streamlined operations and/or merged. A few are becoming increasingly self-supporting through product sales, licensing and research contracts, often starting first by quickly developing products such as diagnostics kits [For further treatment of these issues see [Sercovich and Leopold (forthcoming)].

One additional and important entry barrier to be singled out concerns management skills. In all DBEs there is a tension between the scientific and the business approach. Only those companies that have been able to overcome such tension have succeeded. This based on setting professional managment criteria, usually through hiring people trained in LECs who then impose procedures, organization, planning and structure and narrow substantially the margin for individual autonomy and discretionality. For scientists-entrepreneurs this has often meant leaving their jobs and returning to academia. Companies that have not taken this bitter step have either gone bankrupt, been taken over or remained research boutiques [for a vivid description of this see [Teitelman (l989)].

The area of vaccines provides one of the most dramatic illustrations of the critical importance of threshold barriers and other non-science- related considerations that prevent taking societal advantage of the new biotechnology. Plainly, as long as technological and manufacturing barriers are not lifted, a number of vaccines that can be produced today on the basis of existing scientific knowledge just will not reach most of the world population. Because DC markets do not justify their commercial development, they remain expensive; and because they are expensive, they cannot be afforded by those countries that need them most (see, below, section III.v.).

LDCs have no choice but to pay full attention to such barriers, rather than letting themselves be carried away by the marvellous, and yet unfulfillable, promises of the new biotechnology.

III.iv.ii. Threshold factors

III.iv.ii.i. Research and Development

As already pointed out, R&D-related threshold factors, among others, are bringing about a wave of mergers, acquisitions and consolidations [US Department of Commerce (l989:16-1)] as well as strategic partnering agreements. Biotechnology is part and parcel of this process of industrial restructuring.

DBEs display an unusual R&D intensity. Thus, for instance, in l988 US companies like Cetus, Genentech, Centocor and Amgen had rates of R&D expenses on sales of 21.9, 34.6, 61.3, and 89.5% as compared with 8.2% for the "Drug and Research" industry as a whole [17]. This can also be compared with the computer industry, whose corresponding coefficient is 8.2 per cent and where, at the most, companies spend 21.1% of sales on R&D [*Business Week Scoreboard* (l989.f)]. Because, save exceptions, DBEs have almost no income from product sales, their high R&D expenses must be financed out of interests on liquid assets, royalty fees, research contracts and RDLPs, which normally places them under severe financial strain.

In biotechnology, R&D costs may account for a high percentage of total costs. For instance, Cetus has reported that, in the development of an unidentified, typical, therapeutic protein, production costs accounted for only 8 per cent of an estimated $25 million total cost before marketing. Most of the remainder was made up of R&D expenses [Rukstad (l987:3)]. From this it might be inferred that what matters most to be competitive in biotechnology is to have an efficient R&D operation. However, though necessary, this is by no means a sufficient condition.

Because of demand elasticities and intense R&D competition, reaching the market with a specific product may not be enough to recover sunk R&D investments: it is also necessary to reap economies of scale and scope both in R&D and in production. In this LECs have a comparative advantage except perhaps vis-à-vis DBEs operating in niche markets with low threshold factors.

III.iv.ii.ii. Production

If the promises of the biotechnological revolution are realised--and it appears to be just a matter of time ultil they are--breakthroughs should eventually lead to problems of scaling-down rather than to problems of scaling-up. But this is not yet the case.

For instance, through protein engineering techniques, artificial enzymes might be produced and implanted in cells so that reductions of almost 90 per cent in the current size of bioreactors could be accomplished. But things such as this are still a long way off, among other reasons because the proteins that result are composed of very large molecules and this hinders the extent of their potential use. In the meantime, the problem is how to go from the lab to effective mass-production--ie., how to scale-up the new production processes.

The biological sciences have undergone progress at such a dramatic pace that the capacity of the engineering sciences to digest such progress technologically has been overwhelmed. This is particularly so with regard to purification techniques, the major cost item for biotechnological manufacturing.

One of the main problems to be overcome with regard to scaling up and operation is to make chemical engineers join biochemists in the development of effective downstream processing technologies [Wang (l988):3].

So far, progress in biotechnology has undoubtedly responded to strong "science push" forces (that, in the case of the US, is often related to the strength of the scientific and financial establishments and the idiosyncratic US approach towards health care) [Kenney (l986.b)]; [Teitelman (l989)]; [Johnston and Edwards (l987)].

As a result, as already pointed out, efforts have been focused mainly on what is scientifically possible, rather than on what is technological feasible and, even less, on what is economically profitable. Costs have not received enough attention [OECD (l988:10)]. Before the new biotechnologies even begin to become widely diffused, such priorities will have to be turned upside down.

Only recently have companies begun to focus on the economic and engineering constraints to competitiveness. This has a number of implications as to how quickly the potential advantages of biotechnology products and processes vis-à-vis established products and processes will materialize (see further below section on competitiveness).

One thing to consider from the outset is that production scaleup does not become necessary only once all the lab stages, regulatory procedures and clinical trials have been completed. Clinical trials *per se* already demand scale-up investment. The need to pre-empt markets in intense rivalry situations as is the case in biopharmaceuticals, also leads to an early set up of manufacturing facilities, involving tackling, at an early stage, the engineering and technical problems involved.

The lead times involved in going from the lab to the market are indeed substantial. Let us consider the case of a new enzymatic process. Even disregarding the regulatory constraints that sometimes add substantially to development costs and time (see section III.iv.iii), it takes between one and two years just to complete the laboratory tests involved in such a process. Then, between three and five additional years are required to reach commercial production. Total innovation lead time in this particular case: between four and seven years. In the chemical and pharmaceutical industries they amount to between 7 and 10 years [18].

Human insulin was the first drug ever produced using rDNA technology: it demonstrated conclusively that the technology could be successfully scaled up. It did not show, however, that scaling up is a trivial step. In fact, the attainment of an efficient scaleup is a major actual or potential entry barrier in all the important biotechnology segments.

A number of remarkable achievements in biotechnology have already been made, particularly by DBEs: for instance, in using rDNA technology to produce therapeutically useful proteins and specialty chemicals; hybridoma technology for diagnostics; and, large-scale cell culture for both hybridoma and mammalian cells. DBEs have also attained scientific and technological advances in new hosts and expression systems, immunology and molecular studies of cancer and cloning of plant cells.

However, only in a few cases have such achievements gone beyond the lab and testing stages. These breakthroughs raised enthusiasm among all kinds of investors and money has been pouring generously into DBEs. However, already by 1983 disillusionment started spreading, when it was realised that lead times in commercializing the products of biotechnological R&D where going to be even longer than originally anticipated and that, as a consequence, substantial payback delays were involved.

Scaleup implies a costly procedure involving the passage from the lab to the pilot plant and then to a manufacturing plant where appropriate recovery and purification operations must be designed. Genetic engineering has facilitated mass production of proteins. It also serves as the basis of process innovations that decrease the cost of existing fermentation products such as enzymes and amino acids. But it does not substitute for more traditional engineering disciplines that must be brought into play: ie, chemical, mechanical, process and production engineering.

Relative prices and absolute entry costs have led to applications focused on high value-added products, as well as to progressively more systems-oriented approaches whereby genetic engineering, mutagenesis, optimization of fermentation processes and transformation of downstream products are integrated [19].

As already pointed out, some biotechnology segments are easier to enter than others. Thus, for instance, production of *in vitro* diagnostic kits does not involve investment in sterile fermentation plant, which is required for rDNA pharmaceuticals, making it more feasible for a DBE to be competitive in diagnostics than in biopharmaceuticals.

Mab applications often do not take long to develop, are relatively easy to produce in large quantities and are low cost. But even in this case, financial over-commitment and a high burn rate may impede the DBE in remaining in control of its technological assets, as the experience of Genetic Systems dramatically illustrates [Teitelman (l989:72]. RDLP's are often used to finance clinical trials and scaleup (which are thus subsidized with tax-payer's money) [Kenney (l986:164/6)].

The cost of supplying Mabs to manufacture in vitro diagnostic kits is assessed at $3.5 to $4 million over a 3 year period. But developing the final diagnostic kit may cost 5 to10 times as much [USOTA (1984:150)].

Some potential applications such as single cell protein or commodity chemicals require massive investment in plant and this has been one of the factors contributing to the lack of investment in these areas (see ICI experience, further below).

That scaleup is a bottleneck in biotechnological development is made clear by the increasing interest of OECD governments in devising ways and means to support this kind of effort by industry. Such is the case, for instance, in the US, Japan and the UK. In the latter country, two research institutes and various companies are involved, via the so-called "downstream processing club" in carrying out research into improved separation and purification of products from bioreactors .

Direct support to scaleup is considered one of the most relevant policy issues in the US [USOTA (l988:14/22)]. Japan paid attention to scaleup related problems very early in the development of biotechnology [US Department of Commerce (l984)].

Uncertainty as to the choice of techniques entails further complications in the scaleup process. Although investment in biotechnology industrial plant is rather flexible (it can be used to produce a wide variety of substances depending on the substrate and micro-organism and the same unit processes can be used for recovery of a range of substances), every product produced by fermentation or cell culture requires a specific process tailoring or optimization including at the recovery stage.

Each rDNA product calls for a particular expression vector for the encoding gene. This means that each rDNA product entails a specific process at the molecular level, even though other products may require similar items of equipment and unit operations. The fact that there are several routes (host organisms and expression systems) to produce any substance, impedes any unique one-to-one relation between rDNA product and process. **The process must be customized to the product** (as Table 5 shows, there are clear trade-offs among expression systems; for instance, *E. Coli* is higly appropriate for the scaleup of recombinant cells but its post-translational performance is rather poor while mammalian cells present the opposite case). In addition, patentability of expression vector systems may make them either unavailable or available only at a high cost [Daly (l985:114)].

Although relatively lower value added products that can be produced by the biotechnology route, like vitamins, enjoy large markets, they require expensive scaleup in capacity of the fermentation vats and other equipment [USOTA (l984)]. This, plus the need to recover sunk R&D expenses at the soonest possible time, leads to an in-built selectivity of scaling-up efforts in DCs in favour of high value added products.

One of the problems in dealing with the relation between unit costs and size of market in planning and optimizing scaleup efforts in biotechnology is that engineering cost estimates of economies of scale are not readily available. To make matters worse, many items of equipment must be custom-made so that their performance standards are not amenable to extrapolation. Hence, only sunk R&D costs are available as a proxy, but this leaves out the economic justification of scaling-up procesess from lab to commercial scale. And, although, as said above, the share of R&D costs in total costs is substantial at this early stage of development of biotechnology, the balance can be expected to change over time in favor of a greater share of engineering and manufacturing costs in total costs as the technology matures.

Table 5

Comparison of Commonly-used Expression Systems for rDNA

Criteria	(Bacteria) *E. Coli*	(Yeast) *Saccharomyces cerevisiae*	(Mammalian Cells) Chinese Hamster Ovary
Post-translational changes			
Secretion	+	++	+++
Folding	+	++	+++
Modifications	+	++	+++
Scaleup of recombinant cells			
Yield of product	+++	+++	+
Inducible expression	+++	+++	+
Ease of scale-up	+++	+++	+
Stability of yield	+++	+++	+
Consistency of performance	+++	+++	+
Biology of substrate			
Residual DNA	+++	+++	+
Viruses	+++	+++	+

+++ most acceptable
++
+ least acceptable

Source: Ellis (1989:173)]

The consequences of being overoptimistic with regard to scaling up problems are illustrated, for instance, by Genetic Systems in its failed attempt at handling commercial operations by means of a pilot plan [Teitelman (l989:167)].

The increasing importance being attached to scaleup efforts, and the resulting promise of an interesting market, is underscored by the involvement of several engineering contractors, like Fluor and Stone & Webster in biotechnology operations. Fluor is a partner of Genentech, while Stone & Webster has a collaboration agreement with Biogen.

According to a report world biotechnology scale-up projects will total $8.5 billion during l986/90, $13.1 billion for l991/95 and $20.1 billion in l996/2000 [Business Communications (l988)].

Although many observers suggest that genetic engineering will be widely used for the production of high-value products such as pharmaceuticals, the source just quoted maintains that gene-spliced drugs will be produced in much smaller quantities than conventional products made by organic synthesis and thus capital investment in biotechnology projects may not be as high as assumed earlier.

The experience of a company like Hybritech provides a good example of how the key to business success does not necessarily lie in the importance of the inventions to be exploited but, rather, on apparently trivial pursuits and prosaic innovations: even in biotechnology the triumph of the tinkerer's craft may be the key to entry [Teitelman (l989:176)].

III.iv.ii.iii. Marketing and Distribution

Agrichemical and pharmaceutical multinationals have a clear comparative advantage over DBEs in marketing and distribution.

Marketing and distribution is a major entry deterrent barrier in biotechnology: it has forced DBEs to have their products distributed by LECs with sizeable sales forces.

Many of the drugs being developed by DBEs are to be prescribed by specialists rather than by general practitioners. Hence normal arm's length distribution channels are not accessible (although this may not apply to niche markets). Consequently, DBEs may: (i) license their technology to LECs with access to distribution channels (like Genentech with E. Lilly in human insulin and Biogen with Schering-Plough in alpha interferon); (ii) market through the LECs (like Genentech with human growth hormone abroad); or, more rarely, (iii) market their drugs directly to a select group of specialists (Genentech with human growth hormone and t-PA).

In chemicals, access to distribution channels is easier than in pharmaceuticals. A small number of companies may hold a large share of the domestic market for say an industrial enzyme and a DBE can thus distribute its product directly to end users without a marketing team.

III.iv.iii. Regulation and Public Opinion

Biotechnology process and product lead times and costs are strongly influenced by regulation and public opinion. Regulatory uncertainty is one of the most important barriers on the way to commercialization of biotechnology breakthroughs, since the latter are largely applied to highly regulated industries, such as food and drugs or to other uses that affect public health [USOTA (l988)]. Regulation may be accounted for as a factor that weakens the competitiveness of biotechnology products vis-à-vis existing ones, thereby generating a delay in their timing of introduction and rate of diffusion.

Comparing Europe with the US, regulation is less strict in pharmaceticals and more strict in agriculture. This obviously affects the timing of introduction and pace of diffusion. Thus, for instance, new biopharmaceuticals tend to be distributed in Europe earlier than in the US. (*Bio/Technology*, Vol. 7, Oct 89, l096). On the other hand, as already pointed out, European companies are holding back on herbicide-resistant crops, partly in response to pressures from environmentalists [*Chemistry in Britain* (1989:1210].

Regulatory constraints are highly industry-specific. For instance, when compared with industrial applications such as therapeutics, plant-agricultural and environmental applications of genetic engineering present particular regulatory problems. For one thing, in agricultural applications the organisms are generally engineered for resistance so as to be able to perform their designated functions, while in therapeutical and other industrial applications organisms are usually intentionally weakened. For another, in the former case planned environmental release of rDNA organisms occurs, whereas in the latter all attempts are made to contain the engineered strains [Teso and Wald (l984:17-21)]; [Kingsbury (l988:S39-41)].

Whereas in health-care applications public opinion--at least as expressed by activist groups--has provoked an acceleration of the regulatory process when it is linked to life-threatening diseases (AIDS is the most eloquent example), in the case of agricultural applications, public opinion has served to push regulatory agencies in the direction of conservativism and lengthy procedures [20].

In association with the above, it should be recalled that while drugs reach the public through a professional intermediary, a doctor with a recognized expertise (whose exercise is constrained by considerations of accountability and insurance coverage and liabilities); the intermediary in agriculture, the farmer, does not have much expertise--if any at all--in safety related issues and therefore cannot allay public fears [21].

Particularly in the case of agricultural applications, regulation and public opinion presently rank high on the list of barriers in OECD countries, a situation that may change as regulatory uncertainties as well as public malaise are overcome and as agricultural biotechnology itself moves decisively beyond the R&D phase.

Let us now consider how recombinant microbial pesticides and engineered pest resistant plants fare as compared with chemical control agents [22].

For chemical pesticides, the US Environmental Protection Agency (EPA) decided in 1988 to make regulatory procedures more stringent and costly. New data concerning toxic secondary effects as well as negative environmental effects of certain molecules led to the establishing of a "red" list. For the first time companies must not only submit relevant toxicological data to EPA but also cover the expenses of having such data analyzed. Registration fees for a new chemical cost $184,000 per product, and annual renewal can be as high as $35,000 [*Chemicalweek* (1988:70)]; [*Biofutur* (1989:59)]. Like in pharmaceuticals, regulatory time frames run at an average of between seven and ten years [Burrill (1988:157)].

Even prior to the 1988 amendments, regulation of chemical pesticides had become increasingly burdensome. According to the U.S. government, expenses related to stringent toxicity tests and to the difficulties in finding acceptable new products have pushed the average R&D costs for a new pesticide over the $50 million mark, as compared with $6 million in 1976. In fact, such are the ramifications of restrictive regulation that agrichemical industry analysts consider it, again like in pharmaceuticals, to be a critical factor in the large-scale and ongoing trend towards industry consolidation [US Department of Commerce (1989:12-12/13)]. Regulatory obstacles are also associated to the agrichemical industry's pursuit of biotechnological alternatives (see section III.iii.).

At $64,000 per product, the cost of registering new microbial products is considerably less than for new chemical pesticides [*Chemical Week* , (1988:70)]. But here is where the advantages appear to end. Regulation of recombinant microorganisms, in particular as it relates to environmental release, seems to be a regulatory agency's nightmare, as borne out by both the American and European experiences [23].

On top of industry and public opinion pressures, regulatory agencies have to deal with important science and technology-related uncertainties (ie., those created by the risks of uncontrolled reproduction and of spontaneous mutations of released gene-altered microorganisms) [Offut and Kuchler (1987)]; [*The New York Times* (1989.b)];[*The Economist* (1989.b)] [24].

Undoubtledly, LECs' financial staying power, capacity to deal with longer lead times, experience in navigating through sometimes murky regulatory waters, and ability to influence the regulatory processes directly or through lobbying government and intermediate users means that they enjoy an advantageous position vis-à-vis DBEs. The latters' fragility in the face of these entry barriers is one of the reasons why they are driven to seek strategic partnerships with the former.

As mentioned earlier (section II.ii.iii.) bGH is of particular interest within the context of regulation and public opinion: from a regulatory point of view it is seen as a potentially precedent setting case for agricultural biotechnology. In the public arena, it has become a highly sensitive and politicized issue. It is unlikely that any but major corporate players such as those that are in fact producing the hormone (Monsanto, E. Lilly, American Cyanamid, Upjohn) could withstand the multiple and ongoing pressures related to market entry (and it remains to be seen whether, under the circumstances, the lead company - Monsanto - will draw any advantages over first generation swarmers (the case of bGH is treated in more detail in the annex to this chapter).

Public opinion is also making itself felt in the case of artificial sweeteners. The US Center for Science in the Public Interest and other consumer groups are posing questions about studies linking Hoechst's sulfame-k to tumors in rat studies [Leary (l989:C9)] (see sections II.ii.v. and II.iii.v.).

Difficulties of this and other sorts have translated into lengthy regulatory delays that one industry spokesman puts at six to eight years, that is, much the same as those that confront agrichemicals [25]. In fact, lag times, which are also linked to the inherent seasonality of agriculture--outdoor testing can only take place during certain months of the year --, can have and have had a major impact on R&D programming and costs. It is thus not suprising that many companies, particularly among DBEs, are taking a wait and see attitude or simply dropping projects that involve the environmental release of living microbes. In l987, of the 2,500 or so review applications received by the Office of Toxic Substances (EPA), no more than 4 or 5 involved rDNA [Burrill (l988:161-l64)].

Although science and technology-related regulatory uncertainties are not quite as great in the area of genetically engineered plants as in that of recombinant microorganisms, the review process clearly remains on top of the list of entry barriers. In the case of plants, not only seasonality but the time-consuming nature of the science compounds the effects of regulatory delays [Burrill (l988:161)] [26].

As far as public opinion is concerned, recombinant microbial biopesticides and engineered plants face at least as much wariness and malaise as chemical pesticides. Pending a more settled regulatory context and more reassurances from the scientific milieu, it is unlikely that industry will win the public over. In fact, as is underscored by the case of bGH, even surmounting scientific and regulatory difficulties may not, in and of itself, suffice to overcome public resistance.

As already stated regulation as an entry deterrent barrier has a different meaning depending on the sector of application and the type of company. In pharmaceuticals it increases development costs through lengthy and costly clinical trials and favours relatively large companies. Instead, in agricultural applications regulation affects diffusion mainly through imposing uncertainties that deter the flow of finance.

Similarly, public opinion affects certain pharmaceutical applications by creating a pressure to shorten regulatory procedures, while in agricultural applications public opinion tends to retard procedures.

Even a company like Monsanto has suffered setbacks in the regulatory field: such was the case following the EPA decision of May 20, l986 not to permit the company to conduct field tests of a genetically engineered pesticide until further safety tests had been undertaken. Monsanto originally estimated the resulting delay at one year then drastically cut back on this projection and months after the decision still had not announced plans to attempt testing again (*New York Times Magazine* , November 16, 1986).

One of the most recent and dramatic events pointing out the impact of regulation and the influence of public opinion on developments in biotechnology is a Hesse court ruling in West Germany whereby Hoeschst A.G. was obliged to curtail immediately its plan to produce genetically engineeered human insulin. The court upheld a complaint filed by a citizens' group against Hoeschst. The company suddently had to stop construction of a test plant in which it had already invested $32.5 million. According to the court ruling no plants using gene technology can be constructed and operated as long as the parliament does not specifically allow it [Protzman (l989)].

An absolutely opposite move, one that illustrates the diversity of situations within Europe, was recently taken in Denmark. Research and pilot scale operations and cell hybridization were taken out of the limitations previously imposed. In addition, objections to experiments at the R&D or pilot scale would not cause a suspension of activity, as before. One of the main motivations behind these moves is to prevent the wholesale departure of R&D and pilot facilities overseas, which is precisely what is ocurring in Germany [Simpson (l989:6)].

According to one source, Phase III of the clinical trials imposed by the US FDA in the case of pharmaceuticals would account for close to 30% of the total costs of developing a new drug (an A. D. Little study cited in [*The Wall Street Journal* , (l989.a)]. This puts US companies at a relative disadvantage cost-wise vis-à-vis countries with less stringent regulatory requirements.

III.v. Competitiveness of biotechnology products and processes

Biotechnology permits, among other things, the manufacture of proteins by inserting human genes into bacteria, yeast or animal cells. These techniques are intrinsically far superior to previous methods that entailed a painstaking extraction of proteins from vast amounts of animal tissue or searching for new chemical drugs by means of the conventional trial and error screening procedure. In addition, genetically engineered vaccines and biological substances are thought safer than traditional biologics for they are not derived from blood. In theory, this superiority should lead to obtaining better results at the same (or lower) cost or the same result at a lower cost. In this section we shall discuss to what extent this is so.

The relative competitiveness of biotechnology has probably been overstated virtually across the board. As a matter of fact, there is still a very long way ahead before biotechnology's potential competitiveness turns itself into an actual competitive advantage over established products and processes.

A genetically engineered organism may be more demanding and its performance more difficult to control in production than is the case for its conventional counterparts. Once all cost items are considered, including research costs, stringent process and quality assurance requirements (particularly at the purification stage), handling costs, delivery systems, etc., the profitability of biotechnology, either private or social, is by no means garanted within the near future [Eriksson (l986: 153)].

A declining rate of drug innovation has been observed over the last couple of decades or so in the USA: a lower number of new chemical entities (NCEs) is discovered per dollar spent in R&D. There is also a decreasing share of higher unit value NCEs. Because of declining R&D productivity the number of unique products developed remains at a low ebb.

New product introductions have fallen to almost a third of the level they achieved during the l950s [Rukstad (l987)]; [US Department of Commerce (various issues)]. This drop can be explained by both the tough regulatory standards for safety (see section III.iv.iii), and the decreasing returns to the conventional technique of developing new drugs through a random process of screening active organic compounds not normally found in the human body for side-effects and efficacy.

If successful, companies would produce one drug out of a thousand synthesized organic compounds. By the 1980s researchers were reported to have run out of totally new substances that they could synthesize and test. As a results the total costs of researching and developing a new drug increased 5-fold over the 1960s when safety and legal concerns were less stringent than they are today.

Safety/efficacy tests alone allegedly account nowadays for about 60% of the total cost of developing a new drug. And, on top of this, litigation entails what often amounts to a substantial superfluous overhead to remain in the market or an unavoidable way to exit. Continued high R&D costs are expected to decrease even further the number of NCEs developed.

In addition to the above, patents will expire during the course of l990 on more than 80 per cent of the 100 top selling US prescription drugs [Shah (l988:172)].

Hardly any industry appears to be as ripe as this one to welcome the advent of a promising new technological paradigm that could revolutionize production methods, create new wonder drugs, revitalize its competitive strength and, why not, contribute to increase a rate of return that has been kept, despite all, well above the industry average. Unfortunately, things have turned out not to be so simple.

Although rDNA and cell fusion technologies entail a radical departure from traditional bioprocess and chemical based industries, this does not necessarily entail the automatic enactment of a wholly new technological trajectory. In fact, the closer biotechnology products get to the market the more they tend to be controlled by the same companies that dominate those traditional industries [Sercovich and Leopold (forthcoming)]. Ergo, the evolution of biotechnology's relative competitiveness, its potential for incremental improvements and the timing of introduction and rate of diffusion of resulting products depend to a large extent upon the strategy pursued by those companies.

To begin with, LECs are not so eager to scrap their established processes and products (some of them still reasonably or exceedingly profitable, Burroughs Wellcome's anti-AIDS AZT being the last case of a blockbuster), by entering avidly and light-heartedly a still uncertain new frontier. Before these uncertainties are lifted a considerable amount of time will have to elapse, during which LECs are keeping all their options suficiently open.

Although biotechnology offers hope for turning the tide on declining product introductions, scientists compare the still rudimentary knowledge of the human genetic code to Columbus' maps of the new world. As scientific knowledge expands over the next few decades, lab production of tens of thousands of complex, natural drugs would be possible. Biotechnology companies may achieve an astounding 90 per cent average success rate in the lab, but this *per se* does not imply successful market entry.

Biotechnology drugs are more complex than any that could be synthesized organically by traditional methods in the lab. For example t-PA was 240 times more complex (in terms of molecular weight) than Tagamet, the conventional ulcer drug; therefore scientists could not have been able to synthesize t-PA without relying on biotechnology. But t-PA is considerably more costly to produce than its conventional counterparts and it is not clear yet whether its relatively higher efficacy is worth the difference.

Thus, although a cure appears to have been found for the pharmaceutical industry's innovative anemia, it comes as a mixed-blessing--and with undesirable side-effects.

Doubtless, reduced innovativeness and R&D productivity are being partially offset by new biotechnology-based therapeutics, diagnoses and vaccines that open new therapeutical avenues and increase NCEs and the rate of growth and profit of the industry. For example,1984 witnessed a breakthrough in blood tests for AIDS diagnoses and in l985 a second genetically engineered breakthrough took place: human growth hormone. Biotechnology products such as interferon alpha and hepatitis B vaccine are said to be "rejuvenating" the US pharmaceutical industry. [US Department of Commerce (l987:17-3)].

From the standpoint of actual and potential competition it is worth noting that a product approved for one use can be prescribed for any medical purpose. This means that, although marketing authorization is indication specific, there is certain scope for substitutability across indications. This generates certain advantages to first comers which makes the race to reach the market first--and to recover the R&D expenses--intense. However, on average, as many of 80/90 per cent of the drugs in trial turn out to be too toxic or ineffective for widespread use. Therefore, the game is full of risks and uncertainties that have to be factored in.

Biologicals have the advantage over traditional pharmaceuticals that they come with improved efficacy and specificity. But there are serious shortcomings also.

For one thing, they are difficult to discover and produce and, as a rule, can not be administered orally. For another, their production costs are too high (see further below).

Proponents of biologic therapy are moving toward the concept of combining it with chemotherapy in a synergistically-inspired approach where everybody should have something to win. Bristol-Myers provides a good illustration of this approach [Teitelman (I989:213)]

There is an increasing focus on complementarity between conventional human therapeutics and genetically engineered products. One example is a recent agreement between DBE Immunex and Kodak to develop conventional drugs that mimic or inhibit the activities of biotechnology-based proteins. These second generation drugs are expected to reduce side effects caused by biological proteins and may have a potential for oral administration [*Chemical Week* (I988.a)].

Also, some companies are focusing on engineering genes so as to make cells more susceptible to **existing** drugs. One possible candidate to benefit from this is Burroughs-Wellcome's conventional drug AZT, the only one so far proven effective in the fight against AIDS [*Business Week* (I989.e)].

Ways to upgrade traditional pharmaceutical R&D in view of the biotechnological challenge are also being explored. For instance, DBE Nova Pharmaceutical is developing a drug design system intended to shortcut the tedious and expensive conventional hit-or-miss process of screening chemicals in live animals, by focusing on matching receptors obtained from animal brains and other tissue. The company's work is being sponsored by LECs such as Kodak, SmithKline and Hoechst [Bylinsky (I989); Andrews (I990:D8)].

The chemical industry is also accomodating. LECs are actively looking for ways of reducing the cost of agricultural chemicals that are suffering the potential challenge of biotechnological based products...by using biotechnology. For instance, American Cyanamid is sponsoring DBE Celgene's work aimed at "integrating biology and chemistry" to commercially important targets in fine and specialty chemicals by developing the use of enzymes instead of the traditional herbicide intermediates which rely on more costly conventional catalysts such as palladium and carbon [*Chemicalweek* (l989.a)].

LECs are keeping much of what they are doing in biotechnology to themselves [OECD (l989)]. However, they already have committed themselves to fusing biotechnology with the "pill business" or with the agri-chemical business to a greater extent than admitted.

The price of biotechnology "wonder" drugs is so high that they are said to be contributing (together with artificial organs, custom cancer treatments and fertility procedures) to possibly bankrupting the US health care system. The new drugs have so far made treatments **more** expensive, not less. At the experimental level, a biotechnological drug such as interleukin-2 absorbs half of the 128 million spent each year on cancer treatment [*Business Week* (l989.a:750].

This reality is sometimes played down by the sweeping statement that what matters in pharmaceuticals is not price, but quality. This may be true from the standpoint of the individual patient, particularly if he happens to be wealthy. But this is not the issue. The issue is how society is going to afford the overall bill in case these products reach mass markets. If they do not, their social worth may turn out to be negative.

One example of how biotechnology drug pricing (in turn, related to high R&D costs) is limiting diffusion is given by t-PA. Genentech introduced it at $2.200 a treatment. It must compete with synthetic drugs with lower prices. Amongst them is Eminase, launched by SmithKline on Jan 1, l990, at $1.700 a treatment [*New York Times* (Dec 22, 1989)]. "[T]he technology that Genentech, of all the biotech companies, proved so adept at exploiting did not in fact provide to it the dominating edge that its promoters had predicted (t-PA)" [Teitelman (l989:194)].

There are presently two types of vaccines against hepatitis B on the market. Although both are based on viral antigenes, one of them is produced by means of genetic engineering while the other relies on an older technique that consists of isolating the viral antigenes found in the plasma of the infected subjects. The cost of the conventionally produced vaccine was, by end-l988, about 6 francs for the minimum series of applications required (that is, 8 times the cost of the most expensive of the vaccines bought by the World Health Organization in the context of its enlarged vaccination programme). The corresponding price of the genetically engineered version (which is more efficient) was, at the same date, 800 francs [27]. No doubt, WHO has no choice but to adopt the conventional version, unless there is a substantial reduction of the engineered version [Robbins and Freeman (l989:25)].

Thus, the contribution of biotechnology to improved efficacy and specificity entails unaffordable prices for LDC (and also for large segments of DCs' population). Only conventional, mature and relatively less advanced vaccines can reach hundreds of million children in LDCs thanks to the humanitarian action of United Nations agencies and some philantrophic foundations. As far as advanced country based enterprises are concerned, the use of frontier knowledge in this field is, at least for the time being, out of the question (see, however, the next chapter).

At current beef and dairy prices, processes to produce new animal vaccines (ie., shipping fever) and drugs (ie., hoof and mouth disease, blue tongue, rabies) are too expensive for all but the wealthiest farmers. In the US beef industry, estimated value added by embryo transfer to the final price of an animal is only $50, hardly worth the trouble. The potential for overproduction is also severe. BGH can massively boost milk yields and consequently wipe out many dairy farmers (hence we have obstacles to diffusion on the supply-price and demand-overproduction sides).

Edulcorants obtained with the aid of enzymes have already had a very damaging impact on Third World exports, although they still show sensitiveness to relative prices. In the case of thaumatines, whose genes were cloned by Unilever in I983, the price is prohibitive: $16.000 per kilo. Price is still also an important obstacle to the production of the L glucids found in algae and plantains, sugar beets, and linseed and red algae [Antébi and Fischlock (I986)].

Biotechnologically produced vanilla is reported to cost $ I000/Ib against $32/Ib for vanilla beans. However, a new tissue culture process is currently being experimented that is expected to make it eventually possible to produce at competitive prices [*Food Technology* (I986)].

For the time being tissue culture is not an economically viable alternative; laboratory production costs of cacao butter run at about US$220 per kilogramme, as opposed to US$4 per kg. for cocoa beans [Juma (I989: 139)] [28]. It is estimated that to be competitive, cell culture production would have to have a market value of $85 or more per gram. However, increased experience in research and production could make tissue culture techniques more cost competitive in years to come.

ICI's single-cell protein product, Pruteen, reached the commercialization stage but failed to profit financially: proteins from unicelullar organisms can not yet compete with proteins of animal origin, like soja, as animal food ($150 million were spent on this project) [Hacking (I986:98-102)]. However, ICI obtained valuable experience in operating fermentation plants, particularly large-scale sterile plants, which will be used in ongoing projects. In addition, it got back some of its investment through licencing (see section II.iii.iv).

Cultures of cells and tissues and *in vitro* plant propagation may potentially replace cultivated plants in an even more dramatic way (given their wide range of applications) than synthetic chemicals have replaced many Third World cultures such as indigo, jute and natural rubber. *In vitro* cloning of palm oil, for instance, can be used for industrial oils and fats (although doubts exist now as to the impact of palm oil on health).

Whatever the shortcomings in terms of competitiveness still to be overcome, scientific discoveries keep bringing promises of dramatic economic returns to the new biotechnology. For instance, recent breakthroughs in plant biotechnology anticipate the possibility of growing human Mabs in plants that may lower their cost from $5.000 a gram to 10 cents a gram--and, on top of that, eliminate the rejection problem [Blakeslee (l989)].

Annex to Chapter III

Regulation and Public Opinion as Entry Barriers : The Case of Bovine Growth Hormone

As mentioned earlier (section II.ii.iii.), bGH is of particular interest within the context of regulation and public opinion: its commercial use has become a highly sensitive and politicized issue, all the more so since from both a regulatory and a consumer acceptance point of view it is seen as potentially precedent-setting for agricultural biotechnology [29]. It is unlikely that any but major corporate players such as those that are in fact producing the hormone (Monsanto, Eli Lilly, American Cyanamid, Upjohn) could withstand the multiple and ongoing pressures related to market entry (and it remains to be seen whether, under the circumstances, the leading company--Monsanto--will draw any advantages over first generation swarmers).

In the area of regulation, two sets of considerations merit examination, first, those that relate to the actual decisions made concerning the safety of milk from bGH treated cows; and, second, those that stem from the review process itself.

Despite the fact the sale of milk from experimental herds has been approved, as safe for human consumption, FDA's decision to fully license bGH will necessarily involve certain risks. Although available scientific evidence shows that bGH is in fact safe, new scientific knowledge and testing procedures could eventually call into question these findings . One has but to recall the case of the hormone DES (diethylstibestrol) which was used in commercial beef production for 25 years before improved testing methods led to the discovery of carcinogenic chemical residues in treated meat and to the ultimate commercial ban of the hormone [Kuchler and McClelland (1989:12)]. The fact is that, as one source puts it, "no technological innovation has been adopted with all the possible ramifications for human health and well-being understood in advance" [Kuchler et al. (l989:29)].

The existence of these risks implies that, other adoption-related considerations notwithstanding, once marketed, bGH will have to stand the test of time, and, as in the case of so many other health and environment products, producing companies must factor these risks into their strategies. This implies, among other things, that the companies cannot afford to rely too heavily on bGH and they must be prepared to sustain financial losses (including those linked to legal proceedings) well into the life cycle of the product should the FDA revise its judgment down the line.

Concerning the review process itself, as the first bioengineered products under regulatory review that could significantly impact the dairy and livestock industries, bovine and porcine growth hormones [30] involve potentially precedent-setting procedures with regard to the amount and the nature of the data companies must present and the time-frame needed for approval (or rejection). If the recombinant technology used in hormone manufacturing--and not just the hormone itself--is subject to review, both the data gathering and the review process become more time-consuming and, ultimately, more costly [Kuchler et al. (l989:25/26)].

Although bGH may be close to obtaining regulatory approval by the FDA, questions relating to the product's safety and to the socio-economic impact of its use continue to provoke negative reactions among intermediate and final users. These reactions could threaten commercial viability once the drug is registered.

In order to assess the effects of public opinion upon the rate of diffusion, it helps to distinguish between successive users of the product following the vertical profile of the dairy industry, namely: (i) farmers; (ii) the food-processing industry; (iii) food retailers; and, (iv) final consumers. Groups (i), (ii) and (iii) are intermediate biotechnology process and input users, whose concerns are primarily economic. In contrast, final consumers' concerns are primarily health and safety related. Also caught up in the debate are state and local legislatures. The companies planning to market bGH find themselves in the situation of having to deal with all of these instances.

(i) **Dairy farmers**: This group, which is directly targeted by the bGH producing firms, is interested in the economic impact of the additive's use. Of particular concern is:

a. The possibility that more milk in a market that already suffers from large surpluses will further damage the dairy industry;

b. That this excess supply could be further aggravated by consumer refusal to buy milk products from treated herds;

c. That widespread adoption will accentuate the trend towards economic concentration within the US farming community. In l989, farm organizations in dairy states joined with environmental groups in pressuring large supermarket chains into not selling house brands of dairy products from injected cows.

(ii). **Food processors**: Being extremely dependent upon consumer perception, food-processing companies find themselves pitted against the chemical and pharmaceutical firms producing bGH. Kraft and Borden are among processing companies that have refused to use milk products from inoculated test herds (in the case of Kraft, despite two years of lobbying from Monsanto), and pending a change in consumer attitudes, they intend to continue this policy **even if bGH obtains regulatory clearance**.

(iii) **Food retailers**: The position of this group is basically the same as that of processors and in conflict with that of bGH producers. In the summer of l989 five of the nations largest supermarket chains, including 2,300 supermarkets, announced a boycott on milk products from experimental herds.

(iv) **Final consumers**: As one US Department of Agriculture study states laconically: "If consumers judge them unsafe, treated products will not survive in the marketplace" [Kuchler et al. (l989:30)]. There is a large concensus to the effect that, even when embodied in regulation, scientific assurances can go only so far in convincing sceptical consumers of a product's safety. Market studies conclude that in the case of bGH public doubts run high [Richards (l989)]; [*The Economist* (l989.b:27/280]; [*The New York Times* (l989.a)]; [31].

Public pressures have filtered up into the U.S. government. In l989, Midwest dairy states introduced legislation banning hormone-treated milk, and the Vermont legislature imposed a moratorium on bGH's commercial use, while awaiting a congressional investigation of its effects on farmers and consumers.

What makes opposition to the full-scale commercialization of bGH particularly difficult to surmount is that it reflects two different orders of considerations: medical and economic, which takes the form of a de facto alliance between final consumers and family farmers [32].

It remains to be seen how industry will cope with the multi-faceted resistance it now faces and which, assuming regulatory authorization is granted, could have important effects upon diffusion rates and, ultimately, the market viability of bGH. So far companies with vested interests have sought (without apparent success) to win over consumers by obtaining support from the medical and scientific communities [Richards (1989)].

As to farm group boycotts, industry frustration may well be summed up in the words of a Monsanto spokesperson who criticizes "resistance to new efficiences" as attempts to "'fossilize' agriculture on the theory that preserving the ***status quo*** will protect marginal farmers, existing policies and existing interests. "This" he adds, "amounts to a fourth regulatory criterion of a socioeconomic 'needs test', a major threat to research, as well as commercialization". [Carpenter (1989.b)].

As mentioned above, in the case of agricultural applications of biotechnology, public opinion has served to push regulatory agencies in the direction of conservativism and lengthy procedures, and it is likely that this dynamic is at work in the bGH case; the public is aware, and regulatory agencies are aware that the public is aware, that safety assurances have been prematurely proferred in the past for synthetic hormones, pesticides, chemical additives and the likes. The interface between regulation and public opinion clearly represents a major barrier to successful market entry in agricultural biotechnology.

Notes

1: The relative weights of barriers to entry differ across sectors of application. Thus, for instance, in the US funds have been flowing generously fto set up DBEs in pharmaceuticals. In contrast, research in agricultural applications has been harmed by lack of resources. Costs related to scaleup and clinical trials have become important factors affecting competitiveness in pharmaceuticals, while in agricultural applications scaleup is not yet an issue and field trials have barely been legislated.

2: In I986 the USA Academy of Sciences identified 19 infections against which new vaccines, or improved versions of existing vaccines, could reach the market within a few years. But, although US firms know how to develop new vaccines, they "...lack protection against law suits in the event of adverse effects. The potential cost of such litigation removes the profit incentive to proceed with the development of these vaccines". Price competition also seems to be a dis-incentive (see next footnote). [US Department of Commerce (86:17-3)]. Less than 3% of US R&D funds are devoted to tropical disease prevention or cure. Meanwhile, In Africa, Asia and Latin America, 15 million children of up to 5 years old die every year of respiratory infections, diarrhea and other diseases that often are associated with them (paludism, typhoid fever, rougeole, tetanos). Infant mortality in LDCs runs 20% of all live births. Hundreds of millions of people are infected with parasitic organisms. But DCs cannot afford looking the other way vis-à-vis this tragic reality. Thus, for instance, about 5 million US citizens who travel or reside in tropical areas are at risk. Diseases presenting the greatest problems for them are malaria, schistosomiasis and leprosy. At the same time, just in the US there some 300.000 cases of Hepatitis B a year, 50 per cent more than in I978, reflecting the relatively high cost of the vaccines and the consequent lack of comprehensive vaccination programs for children and other high-risk groups. [Robbins and Freeman (I989:22)]; [US Department of Commerce (I987:17-6) and (I988:18-3)].

3: [US Department of Commerce (I986)] states that increased competition is the only way to reduce vaccine prices. Two years latter, the same publication complained that WHO and UNICEF's tenders pose "a problem" because they stimulate intense price competition. See references in the text.

4: Scientists are still searching for empirical substantiation to the theory of the shrinkage in space and of the sequence of amino acids in three dimensions. "The only thing we can do is change one or two amino acids and see what happens. It is all matter of intuition. All this gadgetry is fine...if it were not for the huge vacuum of the theoretical approach" [Ulmer (I986)]. Bottlenecks related to the structure, function and engineering of proteins has given rise to experiments by academia and industry in protein crystallization in space. Although these studies are in the area of basic research, they are of practical interest for commercial biotechnology insofar as protein engineering--the next important step at the biotechnological frontier--requires knowledge of a protein's function, which in turn is determined by its shape. It is not suprising to find sponsorship for these experiments coming from such major pharmaceutical and chemical interests as Du Pont, Upjohn, Eli-Lilly, Smith-Kline & Beckman and E. Kodak [Broad (I989)]. Protein engineering or "atomic biology" represents the current state of the art of biomolecule management and is likely to be the key discipline in the I990s and beyond. However, the frontier is expected to move further thanks to advances in biophysics and neurochemistry that may give rise to still another shift, this time towards bioelectronics and, later, to "quantum biology" [Sjödahl (I989:144)].

5: It is widely recognized that the major reason why plant applications of biotechnology have, on the whole, not moved significantly beyond the R&D phase is that there are serious deficiencies in the knowledge base underlying basic plant molecular biology and techniques for gene transfer. One source characterizes the lack of knowledge as the **"rate-limiting barrier to commercial development"** of plant biotechnology (particularly of crop species), and contrasts this situation with that of the biomedical sciences, where a vast knowledge base has provided the underpinnings for major progress [USOTA (I988:210)]. Underlined in text).

6: The interferon and interleukin-2 "hype" (beginning and mid-1980s respectively) misled magazines like *Business Week* and *Fortune* which failed to acknowledge the problematic realities of immunomodulators such as interleukin-2 as potential products. The technique developed by Rosenberg (a scientist with NIH) turned out to be frightfully expensive and cumbersome. Experimental flows also occurred. Neither cure nor conclusive proof of efficacy was obtained, on top of the development of serious side effects. "Few considered the expense, the effort, and the time necessary to get interleukin-2 to the markets, the crowded field working on it, the effect of a confused patent situation and of licensing deals or limited partnerships when they talked about the coming bonanza. As with interferon, the promise of interleukin-2 may lie in combination with other key proteins of the immune system, say a gamma interferon, a monoclonal antibody, or even a chemotherapy. The fact was, no one yet knew enough about the complex interplay of the immune system to know how interleukin-2 really worked. Interleukin-2, like interferon and most experimental cancer drugs, was a shot in the dark" [Teitelman:189-90].

7: A major effort is being undertaken to overcome these and other scientific bottlenecks, in the form of the U.S. Department of Agriculture's Plant Genome Mapping Project, a $500 million, ten year research enterprise aimed at locating the genes that controls key traits in crops. Research will involve government, university and industry resources [*Agricell Report* (l989.c)].

8: A recent example concerns an attempt by scientists at the Austrian Academy of Sciences to sequentially transform tobacco plants; the second sequential transformation step using T-DNA suppressed expression of genes on the first T-DNA. Finally, despite advances in delivery systems (cf section II.ii.), the genetic engineering of plants has been constrained by the difficulty in regenerating whole plants from callus, cells or protoplasts [*Agricell Report* (l989.a:22)]; [*Trends in Biotechnology* (l988:265)]; [Fox (l989:1004)].

9: This is taking longer than expected, as Genentech's experience with tPA clearly illustrates, precisely because of high relative prices and the needed accomodation by the health system to finance them.

10: The innovative push of DBEs, in turn, will depend, sooner or later, on their profitability (which, in overall terms, has so far been negative).

11: According to a recent study by the National Science Foundation, US corporate R&D spending has **decreased** in real terms in l989. This occurs for the first time in 14 years. At the same time, funds are being shifted from basic research to development of specific products. Cost-cutting through restructurings, mergers and leveraged buyouts, along with high interest rates and focus on short-term profitability are pointed out as the cause of this changing pattern and of the overall decline [Markoff (l990:1)]. In contrast, Japanese companies are emphasizing long-term R&D projects to derive unique products in years to come. Fewer US companies are engaging in basic research. Their focus is on realigning price-sensitive, low margin assets and taking measures to increase productivity and reduce costs so as to keep profit margins up.

12: The production of vaccines in the US has been curtailed over the last few years, despite a rapidly growing world market, allegedly because of high product liability costs. At the same time, the pre-tax profit rate on sales in human vaccines is estimated at 20 per cent, ie., 4 times that in veterinary vaccines. Presently there is half the number of vaccine producers that there was in the early 1980s. Already in l986 there were only 4 human vaccine producers in the US (2 of them producing dpt-diptheria/pertussis/tetanus vaccines). However, "too much competition" is allegedly slowing down the application and diffusion of new biotechnology-derived vaccines to prevent hepatitis, genital herpes, whooping cough, chicken pox and malaria: "US firms know how to develop these new vaccines but lack protection against law suits in event of adverse effects (in fact prices are going up steeply to cover expected litigation costs, F.S/ML). The potential cost of such litigation removes the profit incentive to proceed with the development of these new vaccines" [US Department of Commerce (1986:17.3)].

13: The following are the sources used in connection with the Connaught case: [Benzing, K. (l989.a and l989.b)]; [*Chemicalweek* , (l989.b) and (1989.d)]; [*Wall Street Journal* , (1989.b];

[Mcgee (1989.a), (1989.b) and (1989.c)]; [*La Presse* , (1989.a), (1989.b.) and (1989.c)]; [*The New York Times* , (1989.c), (1989.e), (1989.f) and (1989.g)]; [Owen, D. (1989)]; [*The Financial Post* (1989)]; [March and Wicks (1989)].

14: Mérieux, which had already acquired a 25.2% stake in Connaught from Crown-owned Canada Development Corporation, started up by offering C$ 140 m for an additional 20% stake in April 1988, followed by a C$37-a-share cash takeover bid in September 1989 valuing the company at C$943.4 million fully diluted. This was in response to Ciba-Geigy's surprise bid of C$30-a-share. On top of this, and in response to queries by the University of Toronto, Ciba-Geigy offered C$ 15 million in research contracts to the university over 10 years plus another C$10 million to fund basic research on pharmaceuticals and vaccines in other Canadian institutions and universities. In response, Mérieux made a similar offer of C$15 million which was then upgraded as part of the final package finally agreed in the winning offer as follows: (i) At least C$160 million or 65% of total Canadian and US R&D spending by Connaugh to be spent in Canada; (ii) of that, C$15 million will be spent in Canadian universities and research institutions over 10 years; (iii) an average 25% of the new R&D funds will go to advanced leading-edge biotechnology; (iv) Mérieux will build a C$30 to 40 million biotechnology centre on Connaught's Willowdale site employing about 125 people and create roughly 30 to 50 permanent new jobs; (v) Mérieux will study the feasibility of building a C$40 million Canadian blood fractionation centre with government support; and (vi) it will transfer technology and advanced production methods to Connaught.

15: However, Monsanto itself has just extended its eight-year research agreement with Washington University through 1994, bringing total commitments to almost $100 million. It is the largest research grant between an American company and university ever awarded [*The New York Times* (1990:D5)].

16: Currently many biotechnological process innovations, often embodied in capital equipment, show a labour-saving bias. As the technology is still in a relatively fluid state, standarized special plant and machinery is not yet available, and processes tend to be relatively labour-intensive. Then economies of scale gain in importance together with technological and organizational changes associated with increasing standardization. Cost reducing technical change gains in importance in face of increasing competition. Skill shortages develop, with resulting wage increase pressure and a further search for labour saving innovations. Later on the biotechnological innovations are likely to turn towards energy and resource saving, which is where their greatest potential contribution to wealth creation lies.

17. The statistical association between turnover and R&D intensity in this industry is negative if we include DBEs and positive if we exclude them.

18: If some of the required steps can be avoided, then these lead times may be substantially shortened. Such would be the case, for instance, if a "quick second" could have access to the necessary data concerning all the genetic information required, the nature of the microorganism to be used to replicate it and, even better, if it could have such a microorganism already isolated. If, in addition, it gets advanced information as to which is the most suitable media to grow the microorganism it could save even more time. But, it would still need a lot of additional engineering information on the fermentation, extraction, separation and purification stages which is much harder to obtain-and even more time and resource consuming to reproduce. See chapter IV on the relevance of this discussion for LDCs.

19: For an interesting example of the logic of increasing integration with its influence on minimum scale of investment and raising threshold factors, see the case of the Argentinian biotechnology enterprise Biosidus dealt with in ch. IV.

20: With regard to bio-pharmaceuticals, it is also interesting to note that public opinion affects not just the timing of introduction, but also the conditions of diffusion. A case for this observation can be built around the offensive against monopolistic pricing for AZT. A similar situation may arise in agricultural biotechnology (although for different reasons) when bGH comes to market.

21: In this context, it is worth recalling that Monsanto's efforts to obtain validation for bGH by the American Medical Association.

22: To a large extent, the USA is performing a standard-setting rôle in the area of regulation as embodied primarily in the "Coordinated Framework for the Regulation of Biotechnology". Published by the government's Executive Branch in l986, this document (which is still being amended) is a complex and far-reaching policy proposal which both explains how existing statutes are to be applied to the regulation of biotechnology and indicates how the policies of the various federal regulatory agencies form the so-called coordinated framework. The document also states which review agencies have jurisdiction over which commercial biotechnology products. It is hoped by those involved in the elaborating the policy guidelines that the principles they contain can serve as a model for other countries [Kingsbury (l988)]

23: For Europe, where, pending a Community-wide regulatory framework, policies still vary from one country to another, see, among others: [Ager (l988)] and [Godown (l989)].

24: Because of the potential risks associated with environmental release, R&D aimed at limiting the viability of altered microorganisms is being conducted. Thus, for instance, virologists at Cornell University recently created a baculovirus for biopesticide use that is unable to survive in the environment for more than a few days and whose descendants cannot reproduce the engineered features [Lewis (l989)].

25: Statement by W.D. Carpenter, Vice President of Monsanto Agricutural Company, Technology Division, quoted in [Burrill (l988:175)]. EPA review of work being done on recombinant microbial pesticides, for instance, commences already prior to small-scale field tests, while in the case of chemical pesticides and naturally occurring indigenous microorganisms, such review takes place at the time of large-scale tests. Furthermore, engineered microbials are examined on a case-by-case basis. [Betz (l988:S40)]; [Kingsbury (l988:163)].

26: "Missing a seasonal planting window for an experimental field trial of a plant biotechnology product represents a major risk to be factored by companies into the R&D process, with such factoring affecting, and probably reducing, total investment decisions" [USOTA (l988:211)]. It is estimated that a year of development can be lost because of a month's delay at an important moment in the agricultural cycle, and that a year's delay can result in a 50% reduction in profits throughout the lifetime of a product.

27: The high price of hepatitis-B vaccines is limiting the market even in the US: because it can not be afforded by large sectors of the population, the number of cases have gone up by 50 per cent over the last few years whilst production has been in the decline [US Department of Commerce (l988-18-3)]. At the same time, the number of vaccine producers has gone down by half over the last two decades. Only 4 producers reamined by l986, all of them enjoying monopolistic or quasi-monopolistic positions with profit rates of 20 per cent or over (for instance, diphtheria-tetanus-pertussis and recombinant Hepatitis B vaccines have just one supplier). [US Department of Commerce (l985:17-3) and (l986:17-3)].

28: [Fowler et al (l988)] quotes US $4 per pound for cocoa beans.

29: This it not to say that there are no differences in the issues raised by bGH and other applications of agricultural biotechnology. For instance, bGH obviously does not require the environmental release of recombinant organisms.

30: Porcine Growth Hormone or Somatotropin (pGH), which is also under regulatory review, can significantly increase pork production.

31: According to one l986 study on attitudes toward bGH conducted by the U.S. National Dairy Board, the drug and chemical companies that produce the hormone are considered "the archvillians of the food world". Quoted in [Richards (l989)].

32: An interesting parallel has been drawn in this respect with events surrounding the adoption of pasteurization. By the end of the XIXth century, the scientific community advocated pasteurization as a means of reducing disease-causing bacteria in milk. Both smaller scale farmers and consumers in the US resisted adoption of the procedure. For the farmers it represented an increase in the uneven allocation of benefits, with large dairy plants drawing a cost-advantage from the extended shelf life and accessibility of more far away markets made possible by the technology. And some consumer groups believed pasteurization would jeopardize the quality of milk. The alliance that stemmed from this situation delayed the full nation-wide adoption of pasteurization for some twenty years [Kuchler and McClelland (1989:12)]; [Kuchler et al. (1989:28)].

IV. LDC Entry Strategies and Related Industrial Policy Issues

IV.i. Introduction

We have emphasized all along the need to be precise when talking about "entry" into biotechnology. We have also distinguished different ways in which the concept can be understood.

The question of what standards are to be set in order to define entry into biotechnology is essential to LDCs. Whatever those standards may be, one thing is certain: they should not be loose and self-indulging. LDCs have already suffered enough from incursions into industrialization that, in the end, proved to be illusory.

Clearly, such standards cannot be set without regard to some key dimensions of the problem already discussed, such as gaps in technological mastery and scaleup-related issues. As we have seen, biotechnology's trajectory has so far been focused on the needs of OECD country populations and, within this, on high value added products.

According to an OECD document: "The new biotechnology is clearly a technology **specific to highly industrialized countries**, as much from the standpoint of R&D needs as from that of potential markets. Enterprises will use progress in plant genetics to substitute for Third World plants, which will be increasingly susceptible to being grown in the OECD countries so that concentration of world trade within the OECD will increase " [OECD (l989:11)] (authors' translation from French, emphasis added) [1].

This statement should be properly understood. "Specific to highly industrialized countries" means specifically geared to their needs which, in turn, are related to economic, social, institutional and cultural traits. There is nothing intrinsic in the new biotechnology that makes it inappropriate to LDCs. Quite the opposite. Nevertheless, save localized instances, LDCs can hardly rely on DCs as a source of readily usable biotechnologies, no matter how relevant DC's basic scientific breakthroughs may be to them .

The previously mentioned bias towards DC needs is quite clear across practically all kinds of applicatons. In the medical field, two thirds of drug R&D in the US is spent on cardiovasculars, antineoplastics, endocrine and metabolic disease therapies, central nervous system research and anti-infectives [2]. Fully 20% of the R&D expenditures goes to clinical studies on drugs relevant to these areas. And less than 3% goes to tropical disease prevention or cure. Meanwhile, the rate of infant mortality in LDCs is assessed at 20%, while hundreds of millions are infected by parasitic organisms [US Department of Commerce (l988)].

The OECD standpoint might be regarded as being at odds with those views that suggest that biotechnology is (at least potentially) particularly relevant to LDCs, not just because of the promises it brings with it, but also because of its presumably low entry barriers, ie., its alleged appropriateness or amenability to be used for leapfrogging [Buttel (l984:32)]; [Kenney (l986); [Perez and Soete (l988)]. We have already discussed the nature of such barriers in the preceding chapter [3].

At first sight, the OECD contention is rather hard to argue against, except on purely moralistic and humanitarian grounds--which is not the stand we have presently chosen to take. However, the first part of the statement is a little bit too absolute. On reflexion, there is probably less to it than it might suggest.

We have seen already that we can not talk of a "biotechnology industry" proper since, while its birth is still being labored, there is already a growing trend towards the routinization of the basic techniques, which will most likely render them increasingly application-specific. We shall presently argue that this fact leads to a much more relativistic approach to the problem of how alien biotechnology progress in DC may be to LDCs than that suggested by the OECD document.

The progressive routinization of the basic techniques makes it easier for user industries to appropriate the know-how concerned. If this appropriation takes place by DC-based LECs, then we are referred back to the well-known problems involved in the transfer of technology from them to LDCs. But this does not have to be the case (at least entirely). LDCs have the possibility of undertaking such appropriation directly in connection with those applications most relevant to them (be it in agriculture, food, health care, mining, waste disposal or whatever).

This prospect is not favored at all by the increasing privatization of scientific knowledge in DCs [Kenney (l986)]. Basic scientific knowledge is no longer freely flowing. Nowadays, when scientists are on the verge of a breakthrough, the first thing they do is not publish, but reserve property rights through patenting. And they are being encouraged to do so through their links with the private sector, since their activity has a direct impact on stock market quotations.

However, this problem concerns particularly the cutting edge of the scientific frontier. Short of it, LDCs have plenty of room to take advantage of the already routinized breakthroughs (like gene splicing and pasting engineering).

One of the main promises biotechnology brings with it is that of letting LDCs wean themselves from economic dependence on commodity prices [4]. However, such a promise must be looked at with a great deal of caution for the route to it may be quite elliptic and hazardous.

As "late-late-comers", LDCs should be able to draw some advantage from scientific and technological progress in DCs. The literature on catching-up, although largely inspired by DC experiences, provides solid grounds for such expectations [Abramovitz (1986)].

Abramovitz leaves open, rather subtly, two windows for the leapfrogging hypothesis. However, he makes a point of warning very clearly that one thing is the potential for catching up and another, very different one, is the actual realization of such potential. The latter depends on a stringent set of requisites relating to what he calls "social capability" (which includes such things as facilities for the diffusion of knowledge, conditions facilitating or hindering structural change and macroeconomic and monetary conditions)[5].

LDCs remain relatively backward, despite all the great potential for catching up that they presumably enjoy, precisely because they lack many or all of the ingredients that concur in forming such social capability. From this point of view, there should be no illusions as to biotechnology being an exception. No doubt, many LDCs can put together a group of first rate scientists and, sometimes, at the cost of great sacrifices, endow them with the resources necessary to undertake high quality research (this is well illustrated by the case of Cuba referred to further below).

However, LDCs cannot be expected to reach the world market for high value added products **on this basis**. As late-late comers like Korea, Hong Kong, Singapore and Taiwan and late-comer Japan before them have clearly shown, the key to effectively exploiting the leapfrogging potential does not just lie in the mastery of the scientific underpinnings of a technology, but rather in the mastery of the engineering, industrial and commercial skills and capabilities that make it possible to reach the market competitively [Amsden (l989)]. Although less successful, Brazil and Mexico teach the same lesson [Sercovich (l985)]; [Dalhman (l985)]. Science-intensiveness does not make matters any easier--rather the opposite.

The case of idiosyncratic, LDC-specific needs for which biotechnology applications may be sought, as well as all those instances where the market fails to operate efficiently (like in vaccines or in bGH), merit special consideration regarding the scope for government intervention.

But, no matter how much government intervenes, the fact still remains that entry into biotechnology cannot be seriously considered without paying attention to such things as skills to be mastered, resources to be commanded, products to be manufactured, organizational modes to be adopted, strategies to be pursued and markets to be served throughout all the stages from the lab to distribution to the final consumer.

The above does not signify by any means--particularly after allowing for cross-country differences--that LDCs should focus on "low-end" applications, most of which are still to be developed. It simply indicates the need for paying enough attention to bottlenecks and constraints regarding "high-end" applications, which are being recommended without much ado in some quarters (see, for instance, [Goldstein (l988)]). For some LDC experiences in this respect, see below.

Entry into high level biotechnology research can render extremely valuable services because, among other things, it makes it possible to keep an eye on what is going on at the scientific frontier and, eventually, take advantage of it as a possible quick follower. We shall examine some examples of this further on. However, entry into the research stage without the capability to proceed forward along the innovative chain entails the risk of having the results industrialized elsewhere and, what is even worse, of merely supporting DC' research endeavors (see below) [6].

Over and above the need to bridge the gaps between scientific breakthroughs and technological design, between technological design and engineering development and between engineering development and manufacturing practice, there are also requisites regarding the necessary interaction among the diverse agents of the innovative process. The Brazilian experience in ethanol is perhaps the best illustration of the importance of the systemic and synergistic aspects in biotechnology development [Sercovich (l986) and (l988)]. However, clearly only a few LDCs can afford engaging in an effort on such a comprehensive scale.

Twenty or thirty years will elapse before biotechnology becomes a widely utilized technology affecting many industrial sectors. How can LDCs take better advantage of it over this period? We shall examine first some national experiences and then attempt to tackle some aspects of this question.

IV.ii. Strategic entry options

Let us now proceed to examine briefly some LDC experiences. Two types of entry by LDCs can be distinguished:

(i) Supply-led: This strategy, in turn, is broken down into: (a) science-led and (b) industry-led. Case (i.a) will be illustrated based on the Cuban experience. Case (i.b) will be exemplified by the Argentinian case.

(ii) Market-driven: this case is treated in connection with Brazil.

V.ii.i. Supply-led strategies

V.ii.i.i. Science-led strategy (Cuba)

Cuba is in a position of leadership in the Third World as far as biotechnology is concerned. It also is a textbook example of a science-driven entry into biotechnology [7]. However, Cuba's entry refers mainly to the R&D stage. Although it has developed some production capacity (so far interferon production labs have enough buffy coat to produce 4.0 milligrams a day) it can not reach the world markets because of allegedly deficient quality assurance guarantees. At the moment, we have no way of assessing its cost competitiveness.

The Centre for Biological Research (CIB), established in I982, and the more recently created (I986) Center for Genetic Engineering and Biotechnology (CIGB), are at the core of a network of institutions that participate in Cuba's drive in biotechnology. CIB began with just six researchers endowed with a small lab, with the aim of producing interferon for use as an anti-viral agent. This was a sort of pilot project related to the feasibility of embarking upon a more ambitious programme. By I986 CIB already had 4 labs (genetic engineering, immunology, chemistry and fermentation). CIB produces its own restriction enzymes and, in addition, does research on the synthesis of oligonucleotides, the cloning and expression of a number of other genes, and the production of Mabs for diagnostic purposes.

Right after its foundation, CIB began producing human leukocyte alpha interferon by a conventional method developed by Kari Cantell of the Central Public Health Lab in Helsinki, who assisted the Cubans in adopting the interferon. Later, partly relying on interaction with European research centres (including the Pasteur Institute in France), CIB shifted to the rDNA route [Fransman (I989)].

Relying on [Kenney (I987)], Juma [I989:122)] states that Cuba chose biotechnology "because it is research-intensive rather than capital-intensive". As we have already pointed out , this kind of observation is only relevant if all that we are concerned with is **entry into research**. Juma seems to be aware of this when he emphasizes that what really matters is the promotion of innovation [8].

V.ii.i.ii. Industry-led strategy (Argentina) [9]

Argentina has a small but rather dynamic industrial biotechnology "establishment" which draws on the remains of what used to be a world class biological science base.

The most advanced firm in human health is Biosidus, which is involved in the development and production of interferon by the conventional and rDNA routes, rDNA insulin and various diagnostic tests. Polychaco, another small-sized firm, has developed and commercializes a diagnostic test for the Chagas infectious disease and has several other tests (pregnancy, hepatitis B, AIDS, etc.) under development. There are also a few other firms working in the field of diagnostics, vaccines and micro-propagation.

Drawing on its profitable conventional pharmaceutical operation, Sidus (Biosidus' parent company founded in I938) decided to cross-subsidize its own entry into biotechnology for which purpose it also relied on its incipient experience with biologicals. The firm was enthusiastic about the prospects for process optimization, new product development and the competitive edge it could acquire thanks to biotechnology when it decided to take its first steps in that direction in I980.

Slowly the company was drawn to pour more and more resources into its initial modest interferon project. In order to enter the rDNA route, it found it necessary to learn a series of related techniques such as cell culture, protein purification, Mab production, fermentation, etc. Mastery of these techniques did not make economic sense in order to produce just one product: an increasing drive towards exploiting economies of scope kept permanently expanding the size of the initial project (originally assessed at a total cost of $300.000) [10].

This was a compelling logic that made itself felt as the operation kept escalating in size, and deadline after deadline had to be postponed [11]. What in the beginning looked like "shortcuts" based on copying and extensive use of freely available information, became an increasing need for tackling unexpected bottlenecks and difficulties requiring a good deal of (unbudgeted) experimental work and innovative efforts to learn the basic techniques and then to apply them effectively.

To sum up, the startup of the lab took one year, the isolation of the gene took an additional year, two further years were needed to have it expressed and 2 additional years to optimize the expression. This adds up 6 years even before commercial production could be tackled. Even at this stage, the initial investment had already escalated ten times to $3 million. As compared with the case of a DBE like Biogen, Biosidus did not save much in terms of time, but its investment was sensibly lower simply because Biosidus did not have to develop a new process but only to reproduce a process that was already known. However, this tells us very little about the economics of the project. This experience illustrates the technical feasibility of the project, but its economic rational remains to be shown.

IV.ii.i.iii. Market-driven strategy (Brazil) [12]

Brazil's aggregate energy input used to consist largely of imported oil. This involved considerable national security risks and economic vulnerability for what is today the seventh largest economy in the world. This led to a return to non-conventional energy sources in which context the alcohol programme played a key rôle. The programe made a lot of sense in a country endowed with nearly one fifth of total world arable land and the highest possible level of photosynthetic activity and efficiency on earth.

Brazil's headstart in the field of sugarcane-based ethanol production was thus largely based on natural advantages. But it also relied upon the comprehensive mastery of all skills and capabilities involved in a self-reliant path: ie., those needed to turn out complete package deals, including all stages of project design, execution and startup, process know how, machinery construction, training, technical assistance and planning of integrated agri-industrial operations.

Brazil's advantage also relies on a long experience with batch-fermentation processes. However, its mastery of this technology has consisted mostly of production engineering experience and machinery construction. Brazil does not occupy a position of leadership in frontier biotechnology research. It does enjoy a leading position in terms of accumulated industrial experience but not necessarily regarding standards of technological practice or, for that matter, proximity to the technological frontier.

The alcohol programme sought to control natural processes rather than to engineer them. Thus, Brazil's headstart relates to things such as traditional fermentation process-related control engineering, scaling-up and mass production rather than to manipulation of genetic information. However, this generates a ready and important market for making use of the recent breakthroughs in biotechnology, not just in connection with the alcohol programme (which has entered a rather unfavorable phase) [13] but also relating to the exploitation of diverse biomass sources and other applications.

Brazil's headstart in traditional biotechnologies has, in fact, spun off into what has now become an incipient although dynamic development effort in frontier biotechnologies. These efforts are being led largely by academic research scientists doing basic rather than applied research (there were some 600 of them in biotechnology-related activities in l983). The linkages between these efforts and industry are still weak.

For instance, already in l980, the need was identified to utilize raw materials other than sugar cane as substrates for alcoholic fermentations. Cassava was the best alternative crop. But cassava is a starchy plant and the major microbial alcoholic fermenter, *Saccharomyces cerevisiae* , does not degrade starch. A treatment with purified amylolytic enzymes was thus necessary to release fermentable sugars.

A group at the Institute for Biomedical Sciences of the University of São Paulo began preparing yeast strains containing all the enzymatic activities needed to convert starch to ethanol directly. In l986 they developed a recombinant containing a secretable mouse pancreatic alpha-amylase. After a number of subsequent improvements, a hybrid strain with all three desired genes was obtained. It produces ethanol from soluble starch with 94-per cent efficiency, although its full potential is still unrealized. In a still further development, a pullulanase gene from *Klebsiella pneumoniae* in *S. cerevisiae* was cloned. The introduction of a functional gene for this enzyme would increase the yeast's efficiency of starch utilization [Bialy (l988:1139)].

In a different line of work, the Biotechnology Center of The Federal University of Rio Grande do Sul is currently developing an engineered vaccine for hoof-and-mouth disease.

Besides these efforts at university research centres, a number of enterprises and private sector initiatives are unfolding. The following are some of them:

(i) The Oswaldo Cruz Foundation is producing lab reagents and diagnostics and plants to produce pharmaceuticals;

(ii) Cibran, a locally-owned antibiotics company is incorporating genetic engineering for antibiotics production;

(iii) State-supported Biobras, founded by Minais Gerais University scientists, is involved in a cooperative agreement with Biosidus (see previous sub-section on Argentina) for the production of genetically engineered insulin;

(iv) Biomatrix is another DBE founded by university researchers. It has entered into association with Agroceres, Brazil's largest national seed firm (the Ipiranga group failed in attempts to include US firms in the agreement);

(v) Bio-Planta do Brasil has set up a research center in association with the US firm Native Plant Investment, where some of the best Brazilian bio-scientists are hired. It is controlled by American Tobacco [Sorj and Wilkinson (l988:150)];

In addition, university-industry relationships are being strengthened through initiatives such as Bio-Rio, led by the Rio de Janeiro Federal University. Biomatrix, Brazil's first national agricultural biotechnology company, and Microbiologia Ltda., a supplier of inputs to biotechnology companies, have pioneered private participation. The science park's endowment is expected to grow from an initial $5 million contributed by state institutions, to $30 milion through domestic and international fund raising. In five years fixed investment is expected to amount to $150 million. The park offers an incubator facility, central labs, administrative support and technical services. Labs will provide facilities for sequencing and synthesis of nucleotides, rDNA experiments and scale-up. [Kaplan (l988:16)].

In conclusion, and as was to be expected, these and other national experiences indicate, that: (i) supply-led type entry into biotechnology by LDCs tends to prevail over demand-driven type entry; (ii) within the supply-led experiences, science-push forces tend to prevail over industry-push forces; (iii) most of the action takes place at university research centres; ie., they consist of **entry into research**; and, (iv) there is a pervasive lack of skills and capabilities to bring scientific output into industrial use [14].

IV.iii. Some industrial policy-related issues

The fact that the initial stages in the international diffusion of biotechnology are taking place at a time when (i) international competitive rivalries have acquired an unusual intensity, and (ii) the US, the leading country in the field, is on the defensive and trying to offset its declining competitive power, is a rather unfortunate coincidence for LDCs. Conditions for access to technological know-how are now much more difficult than they used to be during the l960s or l970s. At that time, a lot of knowledge and information regarding manufacturing processes was transferred on a commercial scale. Today, this kind of transfer to LDCs has become rare.

As an example, the US, joined by other DCs, held back support for the UNIDO-sponsored International Centre for Genetic Engineering and Biotechnology (ICGEB) and is leading a tough policy regarding industrial property rights in the context of the GATT negotiations [15].

The rapidly shifting scientific, technological and industrial frontier in biotechnology accentuates the risks and uncertainties linked to LDC moves.

For instance, initial price quotations for biotechnology products are very high since the companies concerned intend to recover R&D costs as quickly as possible. But prices may go down substantially at any time. This makes it rather tricky for LDC companies deciding to get into the biotechnology business to undertake a realistic assessment of future price trends (even though their own R&D costs may be substantially lower thanks to imitator's advantages) [16]

Potential success of attempts at entering biotechnology depends , among other things, on previous experience at the company and country levels (consider, for instance, Brazil's headstart in fermentation-based processes which is unparalleled in Latin America); inter-organizational synergies within the private sector and between it and the public sector; availability of risk capital; innovation financing; linkages between industry and the scientific and technological system; and, scale-up capabilities. In addition, the availability of application-sector specific skills and capabilities may also play a key rôle by allowing an effective use of the increasingly routinized biotechnology tools.

Although LDCs may have little chances of entering directly into high value added product lines involving heavy R&D expenses, they do have certain indirect strategic routes for taking effective economic and social advantage of advanced biotechnology and building up the experience necessary to enter increasingly higher value added products. Such routes include applications regarding: (i) plagues and idiosyncratic diseases; (ii) improvement in the competitiveness of traditional industrial sectors (agriculture, biomass, food and drinks, forestry, textiles, mining, etc.) by enhancing existing product quality and process efficiency; and (iii) developing new products based on traditional industrial sectors.

It would be illusory to attempt entering commercial biotechnology if the required skills, particularly those related to downstream processing, are not available. Thus, for instance, the lack of bioprocess engineering skills may effectively block scaling-up efforts.

The rich variety of agents of biotechnological change in the world market provides plenty of room for identifying and resorting to sources of international scientific and technical cooperation. Many DBEs are eager to engage into technology transfer agreements with LDC-based enterprises. However, it is necessary to proceed with caution since, in most cases, their technologies are still at an experimental stage.

Singapore has been pursuing a shrewd strategy that consists of taking advantage of expatriate scientists and engaging in joint-research ventures [Yuan (l989):26]. This strategy is also applied by other South Asian countries, particularly Korea [Yuan (l988)] as well as by Spain [Simpson (l989):7] [17]. Zimbawe provides still another instance whereby developed country-based scientific work by expatriate scientists is taken advantage of, in this case in the area of DNA probes for salmonella, which causes 3 and a half million deaths each year in children with diarrhea--although in this case it is not clear whether this has been achieved thanks to a deliberate strategy or to sheer chance [*The Economist* (l990:81)].

But joint-research ventures do not necessarily work that way. Thus, for instance, some agreements may allow DC-based corporations to use LDCs research skills and capabilities as a source of cheap inventive labour whose output is subsequently processed industrially and commercially back in the DC [See Ann Thayer (l989:a:7)] and [*Chemical and Engineering News* (l989.b):14] [18].

For example, the Chinese are involved in a joint-research venture while acquiring, at the same time, turn-key, pre-fabricated, biotechnological facilities from a major multinational to manufacture recombinant hepatitis B vaccines [*The Wall Street Journal* (l989.c)] [19].

This black box-type transfer includes among its components highly sophisticated items (such as ultracentrifugation process equipment that brings into play forces hundreds of thousands of times as powerful as gravity).

Examples of LDCs' excellence in biotechnology research abound (see, for instance, [Kaplan (l989:18)] and [Jacob (!989:16)]. There are also many instances of successful applications of the outputs of such research such as Zimbawe's DNA probes for salmonella, Argentina's diagnostic test for the Chagas disease and Colombia's malaria vaccines [Eisner (l988)]. One of the main tasks ahead consists in creating and/or strengthening bioprocess-related skills and capabilities.

IV.iv. Conclusions

The inability to supply products and services at competitive prices (net of infant industry learning-related costs and external diseconomies) means the inability to generate wealth. No matter how creative the efforts involved might be, this kind of situation is likely to lead to a dead end, when the crucial challenge for LDCs consists precisely in being able to create wealth. High value added products make it possible to pass on high costs of research, but for now they do not appear to be the solution for LDCs attempting to enter biotechnology commercially.

Once the basic techniques of biotechnology become routinized, one of the main questions to be addressed is what to do with them. The answer to this question can not be pre-fabricated. It can only result from a learning process whereby the accumulation of scientific, technological and manufacturing skills and capabilities interacts with social needs and market realities.

Among other things, this entails, on the one hand, the carrying out of basic and applied research on a continuous basis and, on the other, setting up the engineering capability that is needed to translate the resulting insights into competitive products. This process will be more and more influenced by the increasing absorption of biotechnology by user industries, whereby its trajectory will progressively resemble that of those industries.

The above is precisely what, once again, the Japanese appear to have understood very early. In their two-stage strategy, the first stage (l981-88) consisted of achieving the mastery of the scientific underpinnings and practical use of the basic techniques of biotechnology. For this, they have taken full advantage of research links with the best centers of excellence in the world. The second stage, which started already while the first was still in progress, consists of acquiring the necessary manufacturing experience through licenses--and then starting to enter the real game as innovators, forging ahead at both the scientific and technological, and the commercial levels [Masuda (l989)].

Notes

1: There are many examples of biotechnology being used to undermine LDCs' comparative advantages. We have mentioned some of them earlier on (affecting sugar, vanilla, etc.). Another example concerns the plant *shikonin* (grown in China and Korea) which, thanks to its medical properties, sells at $4.500 per kilo. Now it is being produced in bulk through tissue culture techniques by Mitsui in Japan. Similar cases concern products such as pyrethin, codeine and quinine.

2: By the turn of the century fully 20% of the US population will be older than 65. No wonder that the needs of this segment of the population are the "**most significant influence that will shape the [US] drug industry**" (Department of Commerce (l989:16-1)] (emphasis added). This can be safely extrapolated for the bulk of the developed world.

3: In an otherwise insightful early paper, Buttel underlines the low capital intensiveness of biotechnology, and adds: "this technology is within the reach of all but the poorest countries of the so-called fourth World...The investments required to establish state of the art biotechnology R&D--**and even biotechnology industrial production facilities**--are far less than, for example, the cost of a contemporary "turnkey" steel or chemical factory" (Ibid) (emphasis added) The same could be said of advanced flexible manufacturing systems and of a good many highly sophisticated technologies! Likewise, Fransman states that "entry barriers into biotechnology **production** are relatively low" [Fransman (l989)] (emphasis added). Fransman bases this assertion on the experience of DBEs. As we have already pointed out, this is an unwarranted extrapolation, since save a few exceptions, DBEs' business is not commercial production but the rendering of R&D services.

4: It is worth pointing out that Australia has focused on this problem as the main target of its policy in biotechnology. In this regard, the circumstances behind Australia's approach do not differ much from the situation of most LDCs [Freeman K. (l989):14].

5: The first one is: "Those who are behind...have the potential to make a **larger leap**" through investing in new capital that embodies the frontier of knowledge without having to replace "technologically superannuated" capital. The second suggestion in this respect refers to the potential for leapfrogging by countries with superior educational systems, forms of corporate organization and managerial outlook [Abramovitz (l986)] (emphasis added). These arguments have been followed up in [Perez and Soete (l989)].

6: For an identification of a number of missing gaps between basic research activities and industry in biotechnology and the drawing up of some policy implications for the cases of Egypt, Thailand and Venezuela, see [Zilinskas (l988)]

7: This does not mean that actual social needs were not taken into account. For example, the interest in interferon was partly related to the outbreak of dengue hemorrhagic fever affecting some 300.000 people in late l980.

8: Almost without any substantiation, Juma states that Cuba has pursued "a similar strategy to that adopted by Japan during its 'catch-up' period" (Ibid). As a matter of fact, Cuba can be said to have done exactly the opposite, by focusing on research instead of cost-efficient process and product design and production engineering. One indicator of "success" used by Juma is that Cuban scientists have been able to reproduce findings already attained by DC scientists. Another is that a technical cooperation agreement was concluded with Biobras of Brazil to exchange Cuban interferon developments for Brazilian microbial production insulin technology. These are very weak indicators of success since their relevance for actual wealth creation is negligible. This does not imply, by any means, belittling the importance of Cuban efforts, including the significant scientific, technological and institutional learning process that resulted from them, under the embargo placed by the US. Because of this embargo, for instance, the Cubans were unable to acquire automated DNA synthesizing machines.

9: See [Katz and Bercovich (l988)]

10: The lack of local biological input suppliers and other external diseconomies accounted for an unanticipated high degree of vertical integration which certainly did not contribute to keep costs under control.

11: The initial operation was very similar to those in Cuba and in Finland except for the fact that it was much smaller. In the beginning, assistance regarding interferon produced through the conventional route was obtained from the same Finnish expert that had assisted the Cubans. Biosidus' lab, initially staffed with 12 people, had eventually to be scaled up to 40 (70 per cent professionals, with some PhDs) leading to the construction of a new lab in l987.

12: See [Sercovich (1986:ch. 7)]

13: See [Ryser (l989:112L)] and [Kandell (l989:A19].

14: See, for instance, [Zilinkas (l988)] for Thailand, Egypt and Venezuela; [Fernández (l987)] for Mexico; [Kumar (l987)] and [Jacob (l989)] for India; [Yuan (l988)] for South Korea, Singapore and Taiwan.

15: So far 41 countries have ratified the Statutes of ICGEB. Italy (which headquarters one of the two ICGEB's facilities--the other is India--is the only rich country that decided to join the project. The remainder includes Spain, Greece and a large number of LDCs from Africa, Asia and Latin America. Interestingly enough, the four Asian "tigers" have also declined to join. On the other hand, several COMECON countries are members: Bulgaria, Cuba and Hungary. The URSS did not join.

16: [Goldstein (l988)], for instance, quotes prices for a number of biotechnology products at a given point in time in an attempt to show how profitable these products are. However, this type of information may be misleading as a parameter to start an investment that may bear fruit 8 years down the line, when prices may be substantially lower, partly because of eroding quasi-monopoly power by the innovators, and partly as a result of a steady flow of secondary innovations.

17: Indeed, the Korean strategy of taking advantage of Korean-born scientists working in public and private centers of excellence abroad is not altogether original. The Japanese have been applying it for years. Just at the US National Institutes of Health over 200 Japanese subjects were working or studying around l984. They were regarded by their country as a resource to be duly tapped in order to favor national objectives in biotechnology [US Department of Commerce (l984):98].

18: Some US-based transnationals appear to be using the allegedly unfair Japanese strategy of taking commercial advantage of US scientific skills and excellence in cutting-edge fields as a source of inspiration. For instance, Union Carbide is sending its scientists to the U.S.S.R. to find commercial applications for Soviet science [Deutsch, (l989)].

19: Another example is the agreement between Cell Technology Inc., a US DBE specializing in immunotherapy, and the Chinese Medical Academy of Science in Beijing. [*Chemical and Engineering News* (l989.b)]

V. A Research Agenda

V.i. Introduction

In this final chapter a research agenda is submitted. Its contents results directly from the discussion in the preceding chapters. It contains four sections: (i) identification of researchable issues; (ii) background research projects; (iii) policy-oriented research projects; and, (iv) a final section on methodology.

The research agenda might be regarded as a component of a broader Program of Policy Research and Technical Assistance in Biotechnology-PRATAB, that is hereby proposed.

The mission of the PRATAB would be to operate as a scanning and early warning system for the benefit of LDCs, by means of the execution and support of technical services and policy-oriented research on biotechnology.

The coordination, structuring and creation of synergies among the so far scattered efforts made by governments and international organizations in the field should be considered as one of its main objectives. PRATAB should also be capable of serving specific country needs at the request of the interested parties. For this purpose, the setting up of a network of data banks and the supplying of consulting and technical assistance services to LDC governments and institutions should be contemplated at an early stage in the setting up of the program.

PRATAB would be sponsored by governments and by a network of donor agencies and international organizations interested in creating the above-mentioned synergies and in furthering specific country efforts. The list should include, in principle, IDB, IDRC, OECD, UNIDO and The World Bank. Other international and regional entities may join later.

The program would establish a network of researchers and policy makers from both LDCs and DCs and officials of the donor agencies and international organizations, so as to facilitate their reciprocal consultations on a periodical basis.

The financing of the program would result from sums granted through research and consultancy or technical assistance contracts in order to carry out specific tasks by the different participating agencies and intervening governments in the context of their ongoing activities, so that overheads would be kept at a bare minimum.

V.ii. Identification of researchable issues

There are basically three areas where research should be undertaken. They are:

(i) The setting of standards as to what entry into biotechnology means and what it demands in terms of resources, time, organization and skills under different internationally competitive entry scenarios that are feasible according to countries;

(ii) The mapping out of strategic entry alternatives appropriate for specific country conditions; and,

(iii) The management of internationally competitive entry strategies at the enterprise and country level.

Research, technical assistance and policy-making efforts addressed at these issues cover a wide variety of areas, some of the most important among which are discussed below.

The relative weights to be attached to each of the lines of inquiry referred to further below can result only from a meeting of the minds of those involved in the activities of the program. These different points are roughly ordered according to the criteria dealt with in the last section of this chapter. They may involve from very little to considerable resources in order to be duly pursued. Relative costs should be assessed as part of the effort aimed at setting relative priorities.

V.iii. Background research projects

Among the background research projects to be addressed, the following should be contemplated:

(i) A methodology to monitor the factors shaping the trajectory of biotechnology and establish what directions such a trajectory is taking at the scientific, technological and industrial levels;

(ii) The identification of gaps and bottlenecks in the state-of-the-art and their impact on the evolution of the different applications;

(iii) An assessment of shifts in the scientific and technological frontier;

(iv) An assessment of institutional mechanisms geared to increase the flow of basic research results to industry without hindrance to either the quality or the usefulness of the results;

(v) An evaluation of the conditions and resources required for carrying forward the output of inventive activity to the stage of actual innovation for specific applications;

(vi) A study of the composition, direction and trends of international transfer operations in biotechnology;

(vii) A review of advanced and developing country policies in biotechnology;

(vii) An appraisal of the nature and relative weight of barriers to entry for specific industrial applications of biotechnology and changes in their relative importance over time;

(viii) An assessment of the evolution of the relative competitiveness of biotechnology applications over established products and processes, with particular attention to the incidence of engineering and manufacturing factors;

(ix) Country and company case studies, including experiences relating to science parks, promotional financial instruments, factors affecting the efficiency of "trickle down" effects resulting from government-subsidized basic research and local development, scaling-up and technology transfer experience;

(x) Research aimed at identifying supply of and demand for skills and capabilities and effective ways to cover actual and potential gaps among them under alternative entry scenarios;

(xi) Cross-country and cross-company evaluations of lead times, cash flow, investment needs and profitability for specific applications;

V.iv. Policy-oriented research projects

Among policy-oriented research projects, the following ones may be worth pursuing:

(i) Identification of mechanisms for the institutional and financial support of the development of specific biotechnology applications, including ways of mobilizing risk capital and finance for new ventures in biotechnology and support for scaling-up efforts and setting up of manufacturing facilities;

(ii) Study and assessment of key instruments, skills, procedures and forms of organization suitable for translating promising basic biotechnology -related scientific results into technically and economically feasible manufacturing projects;

(iii) Identification of effective interactive mechanisms whereby universities, research institutes, enterprises and financial institutions can converge in a common task;

(iv) Evaluation of the effectiveness of, and ways to improve on, existing schemes for international cooperation in biotechnology;

(v) Study of valid interlocutors, channels and mechanisms for access to particular biotechnology inputs and assets so as to generate detailed rosters of specific technology and manufacturing assistance suppliers;

(vi) Monitoring of the timing of introduction and rate of diffusion of the different biotechnology applications;

(vii) Assessment of the technical and economic feasibility of country-specific, idiosyncratic, applications; of those where market failure prevents the international diffusion of know-how; and those that may enhance competitiveness of already established industries;

(viii) Conditions for effective enterprise-to-enterprise international transfer of biotechnologies; [1]

(ix) Monitoring of learning curves and cost and price trends in DC and LDC-based biotechnology firms;

(x) Pre-feasibility studies for the setting up of (national or regional) biotechnology manufacturing facilities (such as for vaccine production).

V.v. Organizational principles and methodological guidelines

The different potential donor agencies have varying sets of criteria and priorities as to how to tackle a program along the lines of the one just suggested. They may or may not want to break up their activities or to engage in a division of labour with the other participating agencies according to the present structure of the proposal.

Thus for instance, we have broken down the activities of the program into background research projects, on the one hand, and policy-oriented research projects, on the other. The rapidity of changes in the structure and behavior of the industry does not allow for such a split to be carried too far since few of the variables with which policy makers have to deal can be considered as constants.

Moreover, the various countries to be involved should be expected to have different perceptions of their needs and, consequently, set their priorities according to heterogeneous criteria.

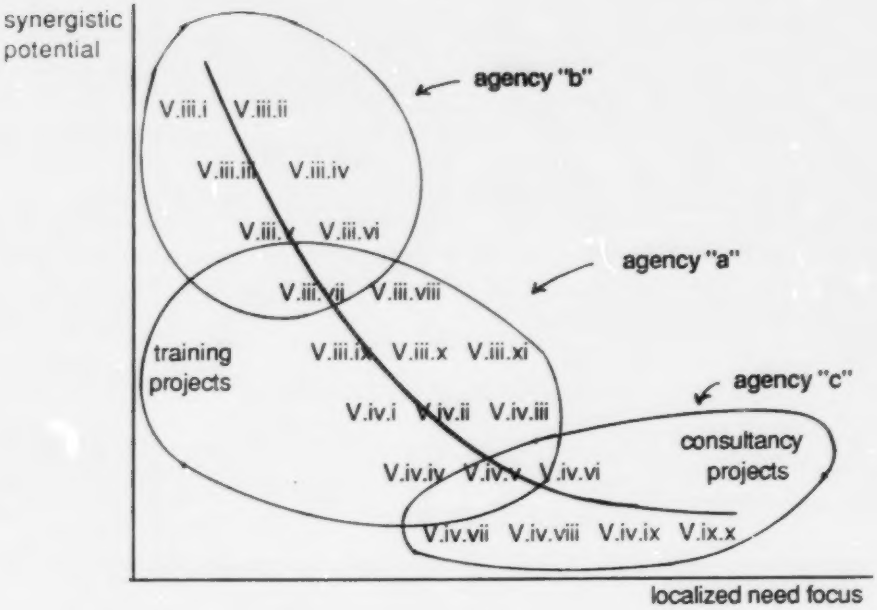
For these reasons, the main thrust of the program should not be to provide ready-made answers but, rather, to offer a methodology, a set of tools and guidelines, to assist in the search for answers. The latter may range from the more general to the more specific.

In deciding upon how to set priorities for the program, a combination of three criteria should be considered. They are: first, the potential for synergy; second, the ability to satisfy localized needs through the actions of the program; and, third, cost.

Graph 1. (see below) provides a first approximation to a possible way to order the different activities and projects proposed according to the first two sets of criteria. It might be hypothesized that donor agencies and international organizations will emphasize the first, while participating countries will concentrate on the second, although this will not necessarily be the case. Finally, the results of the application of the third criteria should be added to the above, so as to come up with a fairly well substantiated set of priorities.

As Graph 1. illustrates, different donor agencies may weigh differently the criteria to be used in order to establish their priorities -- or they may even use a different set of criteria. Thus, for instance, some of them may priviledge a cross-sectional approach, in order to obtain a "sound" mix of synergistic and localized-need focused projects (agency "a"). In contrast, other agencies may chose to maximize synergy (agency "b"), while still others may prefer to maximize the satisfaction of specific needs posed by the participating countries (agency "c"). The extent of the overlapping areas, the value attached to them and budget constraints (see next paragraph) will determine the propensity of the different agencies to engage in mutual cooperation.

Graph 1: Criteria for setting up priorities in the PRATAB
(an hypothetical distribution)


synergistic potential
agency "b"
V.iii.i
V.iii.ii
V.iii.iii
V.iii.iv
V.iii.v
V.iii.vi
agency "a"
V.iii.vii
V.iii.viii
training projects
V.iii.ix
V.iii.x
V.iii.xi
agency "c"
V.iv.i
V.iv.ii
V.iv.iii
consultancy projects
V.iv.iv
V.iv.v
V.iv.vi
V.iv.vii
V.iv.viii
V.iv.ix
V.ix.x
localized need focus

Note: The figures in the graph correspond to the research and related training and consultancy projects referred to in the previous pages. Their position relates to their respective weight of synergistic potential versus localized need focus.

Finally, there is the inevitable consideration of cost. Budget constraints may be regarded as a further weight to be attached to each project. Once again, this weight will differ according to agency and country. This makes the exercise of setting up priorities among the projects on an *a priori* basis an even more speculative task.

V.v. Some final reflections

As already pointed out, it is not easy in practice to distinguish very neatly between "background" and "policy-oriented" research projects, for almost nothing can be taken as a "given". Policy research continuously opens the way to basic questions demanding in-depth research (without which the level of uncertainty may remain higher than acceptable), while the latter may not be duly taken advantage of except by following them up pretty quickly with policy-oriented approaches.

Take, for instance, the case of a "background" research project such as that on gaps and bottlenecks in the state-of-the-art and their impact on the evolution of the different applications. The results stemming from this research may soon be rendered obsolete if no action-oriented guidelines are developed and then promptly followed. Thus, assume that the opening of new, more economic and promising approaches to scale-up is detected, approaches that may be of special relevance to LDCs. If policy-oriented actions aimed at surveying what these new avenues specifically consist of, which companies are involved in such a search, what are the likely channels whereby such an insight may be shared, etc. are not promptly taken, chances are that some opportunities may be foregone. In turn, such policy-oriented actions may raise further questions to be duly researched on more mediate grounds.

This means that there are economies of scope and integration to be reaped from the ability to undertake both background or policy-research oriented follow-up projects, whereby their value may be reciprocally enhanced. Thus, no *a priori* balance between them should be drawn, except on preliminary bases and provided that research can be pursued at the different levels concerned, either by a single agency or through a collaborative arrangement among agencies. A comparative review and careful assessment of what exactly the different bilateral and multilateral agencies are engaged in--and plan to be engaged in in the future--and possible ways to create synergies and complementarities among them would certainly be something welcome in this context.

From an overall perspective, those areas where LDCs enjoy a competitive advantage or have clearly identifiable needs that cannot wait to be met, and where market failure deters and unreasonably delays the international diffusion and application of the respective scientific and technological knowledge, are clear priority areas. But when the knowledge base is in such a state of flux as we have attempted to show in this document in connexion with biotechnology, even the orientations of such a clear criteria cannot be taken for granted and may be subject to renewed uncertainties only to be dispelled through appropriate research efforts.

It would be presumptous on our part to engage in premature generalizations as to policy-research related topics that clearly stand out as particularly pressing since this largely depends upon the specific circumstances of each country. Thus, the bioprocess engineering front may pose more pressing problems for Cuba than for Brazil, while the opposite may be the case regarding the university/industry interface. Only in-depth cross-country comparisons will make it possible to shed some light on this particular kind of issue.

Likewise, some country experiences may be more telling in some connections than others. Thus, for instance, we may learn a lot from the Australian experience, with its highly focused strategy in biotechnology; from Korea's highly successful use of--temporary or secularly-- expatriated scientists and engineers and other cross-border transfer mechanisms; or from Mexico's pioneer efforts in taking advantage of joint-ventures to speed up the transfer of biotechnological know-how.

For these reasons, an effort should be made to identify specific firm- or country-level case studies in correspondence with the nature of the perceived needs for both background and for policy-oriented research projects. This effort cannot be substituted for by any *a priori* -type exercise, ie., without undertaking the necessary consultations with the interested parties.

Finally, let us point out that the level of uncertainty is, in our opinion, still too high to permit engaging into a very ambitious research effort on the economic impact of biotechnology research on traditional LDC exports. However, tentative and well-focused projects should be carried out (for instance, on impact on specific commodities or productive techniques with important social and economic repercussions). But, as long as the the level of uncertainty remains high, these studies should probably put more emphasis on the early detection of changes in the knowledge base and their potential impact on the speed of diffusion than on forecasts of possible impact on employment and world trade.

1: One interesting question in this regard concerns the conditions under which DC-based DBEs are licensing their processes to LECs in general and, in particular, to Japanese LECs. For example, do they reserve their right to have access to whatever engineering information the licensees develop in connection with their processes? If so, how do they actually draw advantage from it?

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